ANTTI J. AHO

The Influence of Frontal Muscle Electromyography on Electroencephalography-Based Depth of Anaesthesia Monitoring

■

ACADEMIC DISSERTATION
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for public discussion in the Main Auditorium of Building M,
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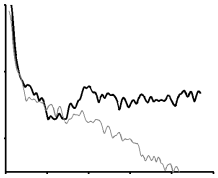

To Merja, Eero and Tatu

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List of original publications

This thesis is based on the following original publications, which are referred to by their Roman numerals I to IV in the text.

I Aho AJ, Yli-Hankala A, Lyytikäinen L-P, Jäntti V. Facial muscle activity, Response Entropy, and State Entropy indices during noxious stimuli in propofol-nitrous oxide or propofol-nitrous oxide-remifentanil anaesthesia without neuromuscular block. *Br J Anaesth* 2009; 102:227-233.

II Aho AJ, Lyytikäinen L-P, Yli-Hankala A, Kamata K, Jäntti V. Explaining Entropy responses after a noxious stimulus, with or without neuromuscular blocking agents, by means of the raw electroencephalographic and electromyographic characteristics. *Br J Anaesth* 2011; 106:69-76.

III Aho AJ, Kamata K, Yli-Hankala A, Lyytikäinen L-P, Kulkas A, Jäntti V. Elevated BIS and Entropy values after sugammadex or neostigmine: an electroencephalographic or electromyographic phenomenon? *Acta Anaesthesiol Scand* 2012; 56:465-473.

IV Aho AJ, Yli-Hankala A, Lyytikäinen L-P, Kamata K, Jäntti V. Can electromyographic arousal be detected visually on the anaesthesia monitor? *Acta Anaesthesiol Scand*. doi: 10.1111/j.1399-6576.2012.02761.x.

Abbreviations

α	alpha (8-13 Hz) activity in EEG (in neurophysiology)
	type I error (in statistics)
ANOVA	analysis of variance
ASA	American Society of Anesthesiologists
BBB	blood-brain barrier
β	beta (13-30 Hz) activity in EEG (in neurophysiology)
	type II error (in statistics)
BIS	Bispectral Index Scale
BIS EMG	bar indicating EMG activity in BIS monitoring
BMI	body mass index
BS	burst suppression
BSR	burst suppression ratio
CNS	central nervous system
C_e	effect site concentration
CSA	compressed spectral array
δ	delta (< 4 Hz) activity in EEG
dB	decibel
ECG	electrocardiogram
EEG	electroencephalogram
EMG	electromyogram
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FEMG	frontal electromyogram
FFT	fast Fourier transform
γ	gamma activity in EEG
GABA	gamma-amino butyric acid
HD	high definition
Hz	hertz
µV	microvolt

ms	millisecond
MUAP	motor unit action potential
NMB	neuromuscular blockade
NMBA	neuromuscular blocking agent
NMDA	N-methyl-D-aspartate
N_2O	nitrous oxide
NS	non-significant result in statistics
P	p-value in statistics
PSP	postsynaptic potential
RE	Response Entropy
RE-SE	difference between RE and SE
SD	standard deviation
SE	State Entropy
SEF 95	spectral edge frequency 95%
TCI	target controlled infusion
θ	theta (4-8 Hz) activity in EEG
TOF	train of four
ZXF	zero crossing frequency

Abstract

During the last 15 years, monitoring the hypnotic component of general anaesthesia has become routine in clinical practise. Several commercially available methods have been introduced for this purpose. These monitors are based on either spontaneous electroencephalogram (EEG) or mid-latency auditory-evoked potentials (MLAEP). These monitors have been reported to decrease the incidence of intraoperative awareness, to reduce the amount of anaesthetic drugs given to the patient, and to reduce recovery time after anaesthesia. The most widely used of these monitors is the Bispectral Index Scale (BIS). Another EEG-based depth of anaesthesia monitor is Entropy. The EEG analysed by these depth of anaesthesia monitors is collected from the forehead of the patient, therefore, rendering the methods vulnerable to confounding factors. One obvious confounding factor is the electromyographic (EMG) arousal caused by the frontal muscles. Also, different types of EEG arousal can produce changes in the numerical values of the depth of anaesthesia monitors without a change in the actual depth of anaesthesia, making the interpretation of depth of anaesthesia monitors very challenging for the anaesthesiologist.

The aim of this doctoral thesis was to study the effect of EMG and EEG arousal on the numerical values of BIS and Entropy, and to investigate if an anaesthesiologist is able to detect EMG arousal visually on the anaesthesia monitor.

In Study I, 31 patients undergoing gynaecological surgery under general anaesthesia were studied. The patients were anaesthetized with propofol-nitrous oxide (N_2O) or propofol-N_2O-remifentanil. The one-channel EEG collected by the Entropy strip was analysed off-line. Intubation of the trachea produced EMG arousal in 13/16 and 15/15 patients with and without remifentanil, respectively. EMG arousal caused a significant rise in Entropy values, even during propofol-induced burst suppression. The EMG activity started at frequencies below 20 Hz, contaminating the interpretation of the Entropy values.

In Study II, 38 patients were studied during skin incision, a typical noxious stimulus. Again, the one-channel EEG collected by the Entropy strip was analysed to discover the incidence of skin incision-associated EMG and EEG arousal under sevoflurane-N_2O or sevoflurane-N_2O-rocuronium anaesthesia. Skin incision caused EMG arousal in 0/19 and 13/19 patients with and without rocuronium, respectively. Skin incision produced EEG arousal in 17/19 and 15/19 patients with and without rocuronium. EEG arousal was classified as beta arousal in 30 patients, causing an increase in Entropy values. EEG delta arousal (two patients) caused a decrease in Entropy values. The power spectra of EEG and EMG overlapped significantly.

In Study III, during light propofol-remifentanil anaesthesia, the neuromuscular blockade (NMB) of 30 patients was antagonized with neostigmine or sugammadex, and the numerical values of BIS and Entropy were studied. The reversal of NMB caused a strong rise in the numerical values of Entropy and BIS in 5/15 patients with neostigmine, and in 5/15 patients with sugammadex. The EEG analysis suggested that the cause for the increasing values was the EMG contamination of EEG. In patients without EMG arousal, no EEG change was seen, and Entropy and BIS values remained unchanged.

In Study IV, the EEG information seen on the anaesthesia monitor of 34 patients under general anaesthesia was recorded with a high-definition video camera, and compared with the one-channel EEG collected by the Entropy monitor. The EMG arousal was only partly detectable on the anaesthesia monitor using 100 μV scale, suggesting that technological improvements to the depth of anaesthesia monitoring are warranted.

In conclusion, the numerical values of depth of anaesthesia monitors are affected by EMG and EEG arousals. EMG arousal and EEG beta arousal increase the index values, while EEG delta arousal decreases the index values. The rise in the numerical values of BIS and Entropy during the reversal of NMB is most likely caused by EMG; however, a small change in EEG may be difficult to see underneath a strong EMG activity. Finally, in order to make detection of EMG arousal more accurate, technological improvements are warranted. However, anaesthesiologists using depth of anaesthesia monitoring should also have the skills to interpret the raw biosignal on the monitor screen, in order to avoid over- and underdosing of anaesthetic agents.

Tiivistelmä

Yleisanestesia koostuu kolmesta eri osatekijästä, jotka ovat tajuttomuus, reagoimattomuus kirurgian aikaansaamille ärsykkeille ja liikkumattomuus. Tajuttomuutta eli anestesian hypnoottista komponenttia voidaan mitata erilaisilla aivosähkökäyrän (EEG) tulkintaan pohjautuvilla laitteilla. Näistä laitteista onkin tullut hyvin suosittuja, sillä niiden on todettu vähentävän leikkauksenaikaisen hereillä olon riskiä ja nopeuttavan anestesiasta toipumista. Nämä laitteet rekisteröivät aivosähkökäyrää potilaan otsalta ja ohimolta. Rekisteröity aivosähkökäyrä muutetaan laitteen toimesta lukuarvomuotoon, ja kullekin laitteelle on annettu suositus siitä, mitä lukuarvoja anestesian aikana tulisi tavoitella. Otsalihasten lihassähkökäyrä (EMG) on yksi häiriötekijä, joka saattaa tehdä näiden laitteiden tulkinnasta vaikeaa tai jopa mahdotonta.

Tämän väitöskirjan tutkimusten tarkoituksena oli selvittää kuinka EMG:n ja EEG:n reaktiivisuus kivuliaalle ärsykkeelle vaikuttaa kahden anestesian syvyyden mittaamiseen tarkoitetun laitteen (BIS ja Entropy) toimintaan. Lisäksi tutkittiin, voiko anestesiologi nähdä EMG:n anestesiamonitorilta paljaalla silmällä, jolloin laitteen antama virheellisen korkea lukema ei johtaisi tarpeettomaan anestesia-aineiden lisäämiseen.

Osatyössä I 31 nukutetun potilaan otsalta rekisteröityä biosignaalia tutkittiin propofoli-ilokaasu ja propofoli-ilokaasu-remifentaniilianestesiassa. Hengitysputken asettaminen aiheutti EMG:n aktiivisuutta yhteensä 28 potilaalla. EMG:n aktiivisuus alkaa jo alle 20 hertsin (Hz) taajuusalueelta. Entropyn mittaamisessa kaikki alle 32 Hz taajuudet oletetaan EEG:ksi eli EMG-aktiivisuus nostaa Entropyn lukuarvoja, vääristäen kuvaa siitä, miltä EEG näyttää.

Osatyössä II tutkittiin 38 potilaan EEG- ja EMG-reaktioita sevofluraani-ilokaasuanestesiassa. Niillä potilailla, jotka eivät saaneet lihasten toimintaa lamaavaa lääkettä (rokuroni), ihoviilto aiheutti EMG-aktiivisuutta 13/19 potilaalla. Rokuroni poisti EMG-reaktion kaikilta potilailta. Lisäksi ihoviilto aiheutti EEG-reaktion yhteensä 32 potilaalle. Kyseessä oli nopeiden taajuuksien (>8 Hz)

lisääntyminen ja hitaiden taajuuksien (< 4 Hz) väheneminen (eli ns. beta arousal) 30 potilaalla. EMG-reaktio ja beta arousal nostavat Entropyn lukuarvoja. Kahdella potilaalla EEG:n hidas toiminta lisääntyi ja nopea toiminta väheni (ns. delta arousal), jolloin Entropyn lukuarvot pienenivät. EEG- ja EMG-taajuuksissa on päällekkäisyyttä, ja tämä päällekkäisyys vaikeuttaa Entropyn lukuarvojen tulkintaa.

Osatyössä III leikkauksen loputtua rokuronin vaikutus kumottiin kahdella eri vasta-aineella (neostigmiini tai sugammadeksi) 30 potilaalla kevyessä propofoli-remifentaniilianestesiassa. Kumoamisen vaikutus BIS:n ja Entropyn lukuarvoihin mitattiin ja yksikanavainen EEG analysoitiin, jotta saataisiin selville, aiheuttaako BIS:n ja Entropyn lukuarvojen nousun EEG vai EMG. Kymmenellä (5+5) potilaalla Entropyn ja BIS:n lukuarvot nousivat selvästi (korkein arvo > 80, normaalisti < 60). Voimakas EMG-aktivaatio näyttäisi nostavan Entropyn ja BIS:n lukuarvoja. Potilailla, joilla ei ilmaantunut EMG-aktivaatiota, ei myöskään ilmaantunut muutoksia EEG:hen.

Osatyössä IV tutkittiin 34 potilaalla, voiko EMG-aktiivisuuden (joka siis nostaa Entropyn ja BIS:n lukuarvoja) nähdä paljaalla silmällä anestesiamonitorilta. Käytettäessä 100 μV asteikkoa anestesiamonitorilla, EMG-aktiivisuus voitiin vain osittain havaita paljaalla silmällä. Tämä havainto korostaa sitä, että anestesiamonitoreiden antamaa informaatiota tulisi lisätä ja niiden resoluutiota tulisi tulevaisuudessa parantaa, jotta EEG-signaalin tarkempi tulkinta olisi mahdollista.

Väitöskirjatyön päätelminä voidaan todeta, että 1) voimakas EMG-reaktio nostaa anestesian syvyyden mittaamiseen käytettyjen indeksien lukuarvoja, 2) EEG:n ja EMG:n taajuusalueet ovat osittain päällekkäisiä, joten niiden erottaminen Entropia- ja BIS-laitteiden algoritmeilla on käytännössä mahdotonta, 3) lihasrelaksaation kumoamisen aiheuttama nousu Entropyn ja BIS:n lukuarvoissa on todennäköisimmin EMG:n aiheuttamaa, 4) anestesian aikaiseen monitorointiin tarkoitettuja laitteita tulee edelleen kehittää, ja 5) anestesiologin tulisi tietää riittävästi anestesian aikaisista EEG:n ja EMG:n muutoksista, jotta vältettäisiin anestesia-aineiden ali- tai liika-annostelu.

1. Introduction

Since mid-1990s, electroencephalogram (EEG) - based monitoring of the hypnotic component of general anaesthesia has become routine in clinical practice. Several commercially available methods have been introduced for this purpose. The EEG-based depth of anaesthesia monitoring has been reported to reduce the risk of awareness and recall during anaesthesia in patients with a high risk for intraoperative awareness (Myles et al. 2004, Ekman et al. 2004), although not all studies have confirmed this finding (Avidan et al. 2008, Avidan et al. 2011). The use of EEG-based depth of anaesthesia monitoring has also been shown to reduce the consumption of anaesthetics (Yli-Hankala et al. 1999, Wong et al. 2002, Kreuer et al. 2003, Luginbühl et al. 2003, Recart et al. 2003, Vakkuri et al. 2005) and enhance the recovery from anaesthesia (Gan et al. 1997, Nelskylä et al. 2001, Luginbühl et al. 2003, White et al. 2004, Vakkuri et al. 2005).

The first commercially available and most widely used of these monitors is the Bispectral Index Scale (BIS) (Rampil 1998). Another EEG-based depth of anaesthesia monitor is Entropy (Viertiö-Oja et al. 2004). The EEG analysed by these depth of anaesthesia monitors is collected from the forehead of the patient, therefore rendering the methods vulnerable to confounding factors. These confounding factors may be physiological, originating from other sources than the brain, or nonphysiological, resulting from external devices.

As the collected biosignal is always a combination of EEG and electromyogram (EMG), EMG arousal generated by the frontal muscles is a potentially confounding physiological factor. Also, different types of EEG arousal can produce changes in the numerical values of the depth of anaesthesia monitors without a change in the actual depth of anaesthesia, making the interpretation of depth of anaesthesia monitors very challenging for the anaesthesiologist.

The behaviour of the depth of anaesthesia monitors' numerical values has been studied in various settings very intensively during the last 15 years. However, in most of these studies, the analysis of the biosignal *per se* has been neglected. The

original biosignal and the spectral analysis of the biosignal have only rarely been compared with the index values.

In the first study reported in this thesis, we studied the effect of EMG arousal on Entropy's numerical values during intubation and beginning of surgery in patients anaesthetized with propofol-N_2O or propofol-N_2O-remifentanil. The second study investigated the effects of EMG arousal, and the effects of EEG arousal, on Entropy's numerical values during sevoflurane-N_2O anaesthesia with or without neuromuscular blockade. The third study was aimed to provide an electrophysiologic explanation to a clinically observed phenomenon that the numerical values of BIS and Entropy increase when neuromuscular blockade (NMB) is reversed with sugammadex or neostigmine at the end of surgery. The fourth study focused on the hypothesis that EMG arousal can be visually detected on the monitor of the anaesthesia work station.

2. Review of the literature

2.1. General anaesthesia

One definition of general anaesthesia is that it is a state of unconsciousness, amnesia and immobility (Antognini and Carstens 2002). In a wider context, desirable goals for adequate general anaesthesia also include muscle relaxation, antinociception, neuroendocrine control, cardiovascular stability, and absence of postoperative emesis and shivering (Urban and Bleckwenn 2002).

The three above mentioned prerequisites for general anaesthesia can be achieved by administering solely one drug, anaesthetic. To block the spinal cord H-reflex, which is responsible for movement response to noxious stimuli, a lot more anaesthetic would be needed than to produce unconsciousness (Rampil and Laster 1992, Antognini and Schwartz 1993). Excessive amounts of anaesthetic cause undesirable side effects (hypotension, delayed recovery, postoperative nausea and vomiting). Therefore, in clinical practice, general anaesthesia usually consists of three different drugs: anaesthetics are given to produce unconsciousness, neuromuscular blocking agents (NMBAs) to produce immobility or reduced muscle tone, and opioids to blunt responses (movement, hypertension, tachycardia, neuroendocrine) to noxious stimuli. By administering these three drugs in reasonable doses, overdosing of anaesthetics and potentially harmful side effects (hypotension, ischemia of the myocardium, nausea and vomiting, delayed recovery) may be avoided. Especially NMBAs are potentially dangerous for the welfare of the patient: after NMBA administration, patient is totally paralyzed and appears unconscious. If the administration of the anaesthetic is for some reason decreased/stopped, the patient may be subjected to intraoperative awareness. Intraoperative awareness is a very traumatizing experience, causing long-lasting psychiatric sequelae (Lennmarken et al. 2002, Samuelsson et al. 2007, Leslie et al. 2010b). Thus, to avoid intraoperative awareness, monitoring of the depth of anaesthesia with EEG-based monitors is highly recommended (Johansen 2006).

2.2. Electroencephalography (EEG)

2.2.1. EEG registering

Electroencephalography (EEG) is a method for registering changes in the electric potentials generated by brain cells. The equipment for EEG registering consists of registering electrodes, analogue amplifier, analogue band pass filter, an analogue-digital converter, and a computer (for reviewing, filtering and storage).

The electrodes for EEG registering are usually located outside the brain tissue, on the surface of the skin of the head. The surface electrode is a plate that transmits the registered changes in ion potentials into recordable changes in voltage. When EEG is recorded in clinical neurophysiology, the electrodes are positioned according to an international placement system (Figure 1). The most recommended electrode positioning system is the International 10-20 system (American Clinical Neurophysiology Guidelines 2006), but also 10-10 and 10-5 systems are used.

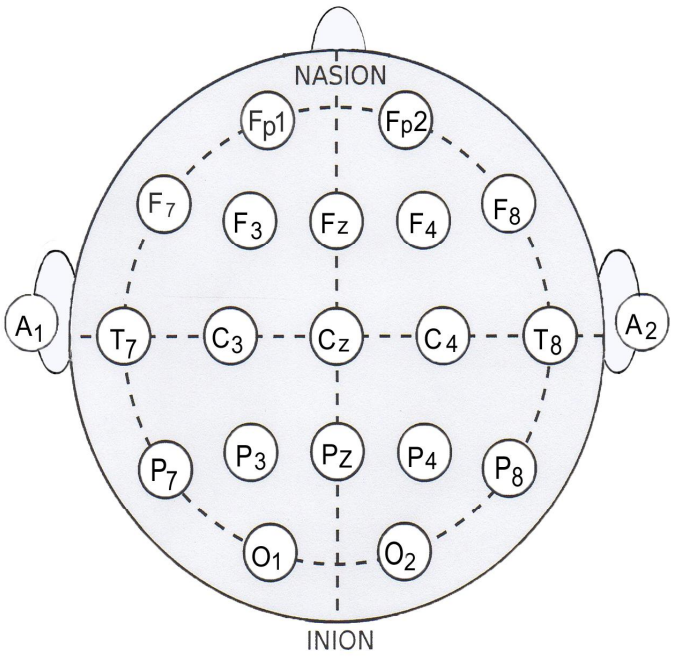

Figure 1. International 10-20 electrode placement system.

First, the recorded analogue EEG signal is amplified in a 2000 to 4000 µV dynamic range, which is sufficient to capture physiologic EEG (< 1000 µV, peak to peak). Then, an analogue band pass filter is applied. The low (high pass) filter stabilizes baseline drift and maintains a normal baseline. The typical low filter settings for digital systems range from 0.01 to 5 Hz. The high (low pass) filter reduces noise above physiologic frequencies and prevents signal distortion (aliasing) during digitization. For routine recording, a high filter at 70 Hz is sufficient, but advanced systems allow high filtering up to several kHz. The transducer converts the analogue signal to a digital signal. Also an analogue notch filter is available, filtering out the 50 Hz (Europe) or 60 Hz (North America) power line artefact, but leaving the majority of the original signal unchanged.

2.2.2. Physiologic basis of EEG

The spontaneous brain activity seen in EEG originates mainly from the cerebral cortex. The cerebral cortex consists of six layers, which are differentiated by their histological dominant cell types (White 1989). The axon potentials cannot be seen in EEG, owing to their short duration (approximately 1 ms). The waves seen in EEG mainly reflect the synchronous postsynaptic potentials (PSP), the duration of which is 10-100 ms. Both excitatory and inhibitory PSPs can be seen in EEG. In order for the intra- and extracellular currents related to synaptic potentials to become visible in EEG, the dendrites of the cells must be aligned parallel to each other. Therefore, the pyramidal cells are the main source of EEG signal recorded from the scalp. The pyramidal cells have short basal dendrites and a long, apical dendrite extending toward cerebral cortex (Figure 2).

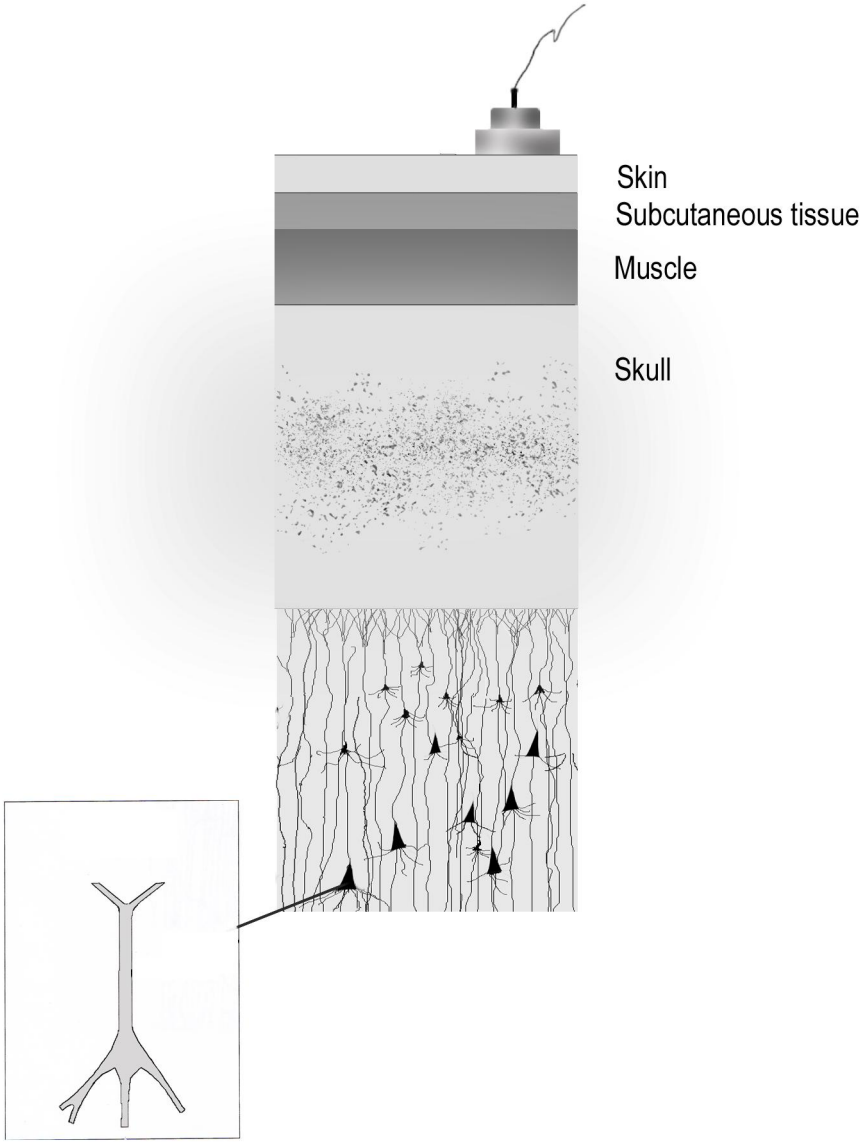

Figure 2. Schematic presentation of a pyramidal cell.

It has been estimated that 10^4-10^5 neurons must be activated simultaneously to produce a signal that is measurable on the scalp. The tissues outside the brain (especially skull, but also cerebrospinal fluid and scalp) weaken the signal and spread it to a wider area (Rampil 1998).

Spontaneous brain activity has been classified into different frequency bands based on the oscillation frequency. The classical frequency bands are delta (δ, < 4 Hz), theta (θ, 4-8 Hz), alpha (α, 8-13 Hz), and beta (β, 13-30 Hz). Occasionally, also gamma band (γ, > 30 Hz) is recognized.

In a healthy adult, δ activity can be seen during deep sleep, especially frontally. The δ activity is most likely a sign of a greatly reduced or absent cholinergic afferent activity. The δ activity is generated in the pyramidal cells, as a result of alternating excitatory and inhibitory phases (Steriade 2006).

The θ activity can be seen in children about to fall asleep, but it is more frequent in lower mammals. Also healthy adults may have rhythmic θ activity, especially near the midline of the brain. The anatomical origin of the θ activity is not fully understood, but activation of limbic areas may produce θ activity (John and Prichep 2005).

The α rhythm is present when person is awake, especially when eyes are closed and the person is relaxed. The α activity is present especially in occipital area. According to Steriade, thalamus is the pacemaker for α activity, and thalamus also controls the cortical epicentres, which can spread α activity on the cortex through cortico-cortical pathways (Steriade 2000).

The β activity is most prominent frontally, when a person is alert or performing a task. It can also be present during light sleep. The β activity is generated by the cortical neuronal networks and, like α activity, is probably controlled by the thalamus.

The γ waves are not usually detected in EEG. The role of γ activity is not fully understood. Recently, it has been thought to play role in multisensory semantic matching (Schneider et al. 2008).

2.2.3. Analysis of EEG

The best result in the analysis of EEG is achieved by inspecting both unprocessed (time domain analysis) and processed (frequency domain analysis) displays, understanding the characteristics and limitations of both methods. In general, when analysing EEG, the focus of the analyst is on 1) the maximal peak-to-peak amplitude, 2) relationship between maximal amplitude and dominant frequency, 3) variability in amplitude and frequency, and 4) asymmetry between cerebral hemispheres (Edmonds et al. 2004).

2.2.3.1. Time domain analysis

The traditional tool for EEG analysis is the time domain analysis. In such an analysis, the time is presented horizontally along x-axis, and the biopotential (amplitude) is presented vertically along y-axis. When time domain analysis is used for diagnostic purposes, the EEG pattern of the patient is compared with known normal or abnormal patterns. The scales of the axes are presented linearly. Owing to the fact that amplitude range can be quite large, in order to be able to visualize low amplitude signals, recording sensitivity must be increased.

2.2.3.2. Frequency domain analysis

In frequency domain analysis, selected segments (epochs) of the original EEG signal are decomposed into their component frequencies. This is achieved by applying a mathematical method, fast Fourier transformation (FFT). As a result of FFT, the power spectrum of the EEG is calculated (Figure 3). The Fourier transformation is also called spectral analysis. The FFT has also its limits; shortening the epoch leads to a reduced number of data points, eventually rendering FFT meaningless. The shorter the epoch, the more differences between the epochs occur. Therefore, epoch lengths of 2 seconds or more are feasible. Epochs of 4-8 seconds are more common (Levy 1987).

The spectral information yielded by the FFT has traditionally been simplified by using univariate (single variable) numeric descriptors. The power in classical EEG frequency bands (delta, theta, alpha and beta) can be calculated in absolute, relative or normalized terms. The most frequently used univariate frequency descriptors are: spectral edge frequency 95% (SEF 95, the frequency below which 95 % of the spectral power occurs), peak power frequency (the frequency containing the highest amplitude), median power frequency, and mean spectral frequency.

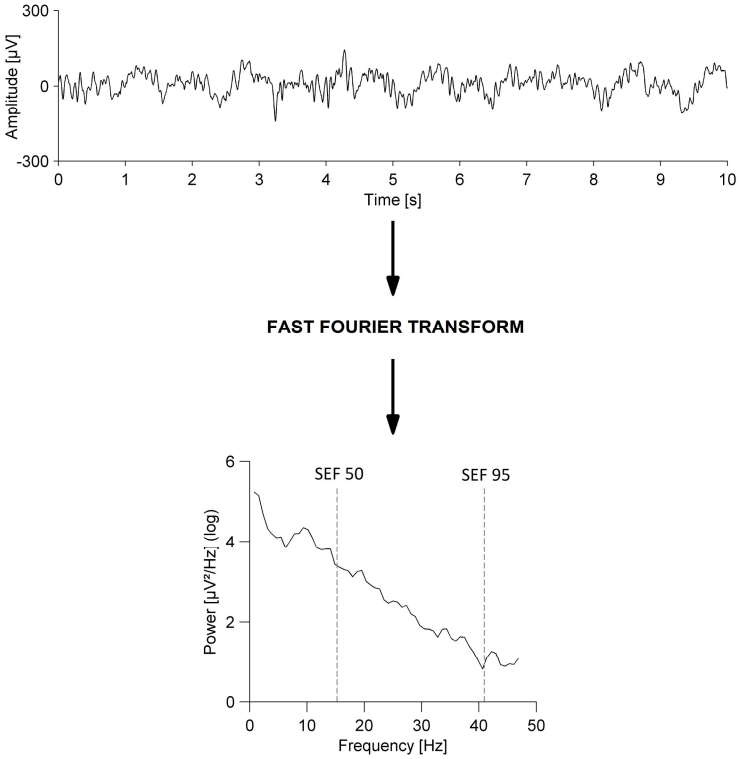

Figure 3. Conversion of time domain EEG to frequency domain power spectrum. SEF 50 = spectral edge frequency 50 % (= median power frequency), SEF 95 = spectral edge frequency 95 %.

Displaying successive power spectra three-dimensionally was originally introduced by Joy (Joy et al. 1971), and later it was named compressed spectral array (CSA) (Myers et al. 1973). Owing to the data compression, CSA has become a very popular display of processed EEG in the frequency domain. Another method utilizing successive power spectra is spectrogram (Figure 4). In both CSA and spectrogram, FFT is applied to produce successive power spectra, usually from epochs lasting 2-10 seconds.

When raw EEG is transformed to frequency domain, the waveform is lost and many non-stationarities or transient phenomena (spikes, burst suppression) remain undetected (Edmonds et al. 2004). Therefore, the time domain analysis of EEG remains the cornerstone of EEG analysis.

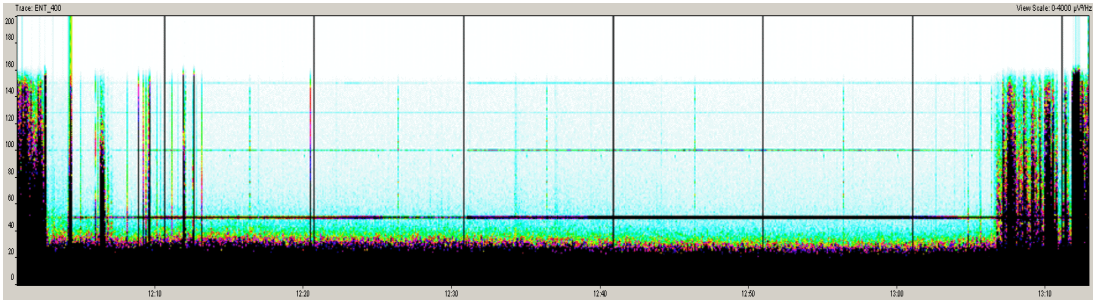

Figure 4. Spectrogram.

2.2.4. EEG during general anaesthesia

During consciousness, the interindividual variability in the distribution of EEG power is great. When anaesthetic drugs are given, the variability decreases. The most frequently used anaesthetic drugs (thiopental, propofol, isoflurane, sevoflurane, desflurane) cause similar changes in EEG, when given in increasing concentrations (Martin et al. 1959) (Figure 5). The change in EEG during general anaesthesia is biphasic (initially a shift to higher frequencies than awake, thereafter a shift to lower frequencies than awake). First, the power in alpha frequency in occipital regions decreases and the power in beta frequency increases, especially frontally. With deepening level of anaesthesia (surgical level), the power in delta activity increases (John et al. 2001), and the power in alpha, beta and theta decreases (Alkire 1998). An increased dose of anaesthetic results in a burst suppression pattern. In this state, low voltage periods are followed by high amplitude activity. If the concentration of the anaesthetic is further increased, the EEG will change to suppression (electrical silence).

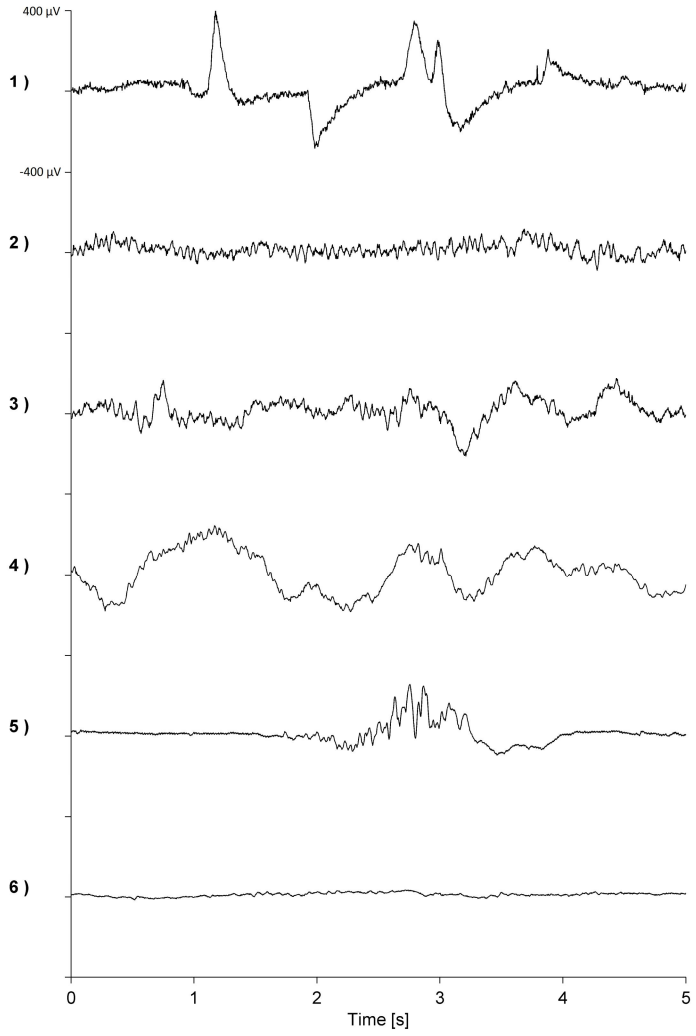

Figure 5. The typical changes in EEG (F_{p1}-F_9, 0.5-118 Hz) caused by increasing doses of propofol. 1) Patient is awake, high frequency oscillations are caused by eye blinks and EMG (spiky appearance) can also be seen. 2) During light anaesthesia, eye blinks disappear and EEG consists mainly of high-frequency beta activity. 3) With deepening anaesthesia, there is a gradual shift towards lower frequencies. 4) High-amplitude, low frequency activity predominates during deeper anaesthesia. 5) Burst suppression. 6) Suppression. The scale is the same (± 400 µV) in all EEG signals.

2.2.5. EEG arousal during general anaesthesia

The EEG arousal was first reported in the literature by Berger (Berger 1930). Berger noticed a shift from alpha dominance (patient's eyes were closed) to beta dominance (eyes were opened). In Berger's report, he used the term "desynchronisation" as a synonym for arousal. In 1949, Moruzzi and Magoun stimulated the brain stem reticular formation of a cat and used the term "EEG arousal" to describe a shift from high-voltage slow waves to low-voltage fast activity in EEG (Moruzzi and Magoun 1949). Later, it has been shown in animal studies that high-frequency stimulation of the reticular formation can produce either EEG desynchronisation or EEG synchronisation (Prince and Shanzer 1966). In addition, Bimar and Bellville have reported that both types of EEG arousal can be seen in humans during surgery (Bimar and Bellville 1977).

In the anaesthesiology literature, the term "EEG arousal" is often used to describe a shift from low frequencies to high frequencies. This phenomenon (desynchronisation) has been called excitatory arousal (Wilder-Smith et al. 1995) or classical arousal. The shift from low frequencies to high frequencies appears to be more common (50 % of the patients, Sleigh et al. 2010). It can be caused by noxious (laryngoscopy, intubation of the trachea, skin incision) or non-noxious sensory stimuli, even during deep levels of anaesthesia. One type of the classical EEG arousal may be the change of episodic patterns (spindle-like activity and burst suppression that are not well described by the FFT methods) into more rhythmic activity (MacKay et al. 2010).

The shift from higher frequencies to lower frequencies (synchronisation) has also been called reverse arousal, paradoxical arousal (Bischoff et al. 1993) or inhibitory arousal (Wilder-Smith et al. 1995). In 2010 Sleigh and co-workers suggested that the imprecise term "paradoxical response" should be replaced with the more accurate term "delta response" (Sleigh et al. 2010). The incidence of delta arousal during skin incision may depend on the type of surgery (Wilder-Smith et al. 1995, Bischoff et al. 1996). Recently, Sleigh and co-workers reported 15 % incidence in delta arousal in a mixed patient population undergoing orthopaedic, abdominal, and laparoscopic surgeries (Sleigh et al. 2010). Also the delta arousal can be caused by noxious or non-noxious stimuli.

The EEG changes in the two types of arousal are opposite: the shift from low to high frequencies causes an increase in alpha and beta activities, as well as a decrease in delta activities (Kochs et al. 1994). Also, the total EEG power may be decreased. The delta arousal causes a decrease in alpha/beta activities, and an increase in delta activity.

Due to the evolutionary significance of remaining alert, multiple parallel ascending arousal pathways have developed. Therefore, the mechanism of and the neurophysiologic explanation for EEG arousal during general anaesthesia are most likely linked to the neuronal pathways of sleep and arousal: from arousal nuclei in the pons, midbrain and hypothalamus to thalamus, reticular formation and cerebral cortex (Franks 2008). A recently published study, in which the loss of consciousness in healthy volunteers was achieved with dexmedetomidine or propofol, suggests that return of consciousness is produced by the activation of the phylogenetically older brain structures (brainstem, thalamus, hypothalamus), not by the activation of the neocortex (Långsjö et al. 2012). This finding may explain the difficulties in detecting awareness during general anaesthesia even when EEG-based depth of anaesthesia monitoring is utilized (Avidan et al. 2008, Avidan et al. 2011).

Although the physiological sleep and general anaesthesia appear to have similarities (Franks 2008), the EEG arousal caused by stimuli during general anaesthesia and arousal during emergence from anaesthesia are not exactly the same phenomenon, *i.e.* the EEG arousal during anaesthesia is not an equivalent of EEG during consciousness. It has been suggested that the stimulation of superficial (mucosa) tissues produces an excitatory (classical) arousal, while stimulation of deeper (visceral, joints, muscle) causes an inhibitory (reverse, paradoxical) arousal (Wilder-Smith et al. 1995).

2.3. Electromyography (EMG) of upper facial muscles

In this section of the review, the properties of EMG that are relevant to the EEG-based depth of anaesthesia monitoring are discussed. Owing to the placement of the BIS and Entropy sensors recommended by their manufacturers, three upper facial muscles (frontal, orbicularis oculi, temporal) are of special interest. If not specifically stated otherwise, the term “upper facial muscles” used in this section of

the review refers to these three muscles. It is essential to keep in mind, that electrodes used in BIS and Entropy monitoring may register EMG also from other muscles located nearby, especially masseter muscle.

For decades, it has been suggested that the upper facial muscle electromyography (FEMG) could be used as an indicator of anaesthetic adequacy (Harmel et al. 1978, Edmonds and Paloheimo 1985, Edmonds et al 1988, Paloheimo et al. 1989, Dutton et al. 1998) or as a monitoring tool for sedation in the intensive care unit (Walsh et al. 2011). It has been shown that the duration of action of NMBAs is shorter at upper facial muscles than at adductor pollicis muscle, the site where NMB is measured in clinical practice (Paloheimo et al. 1988, Hemmerling et al. 2000). Therefore, significant EMG activity can be present in upper facial muscles without any objectively detected signs of EMG activity in the hypothenar muscles.

2.3.1. Physiologic basis of (upper facial) EMG

Many technical aspects concerning the EMG are the same as with EEG. The EMG can be recorded with needle electrodes, but here the focus is on the EMG collected with surface electrodes, as it is recorded in depth of anaesthesia monitoring.

Activation of the motoneuron results in an impulse propagating to the motor endplates that are connected to the motoneuron. At the endplate zone, electrochemical events generate a muscle action potential (AP). The resulting muscle fibre AP proceeds in both directions of the muscle fibre. The muscle fibre AP is also carried through the t-tubule system to excite deeper contractile elements. The muscle fibre AP waveform is related to the histochemical properties of the muscle fibre. Fast-twitch fibres produce APs of greater amplitude and with faster depolarization and repolarization. Fast-twitch fibres have higher conduction velocities than slow-twitch fibres. The action potentials from the muscle fibres innervated by the same, single motoneuron produce a motor unit AP (MUAP) (Figure 6).

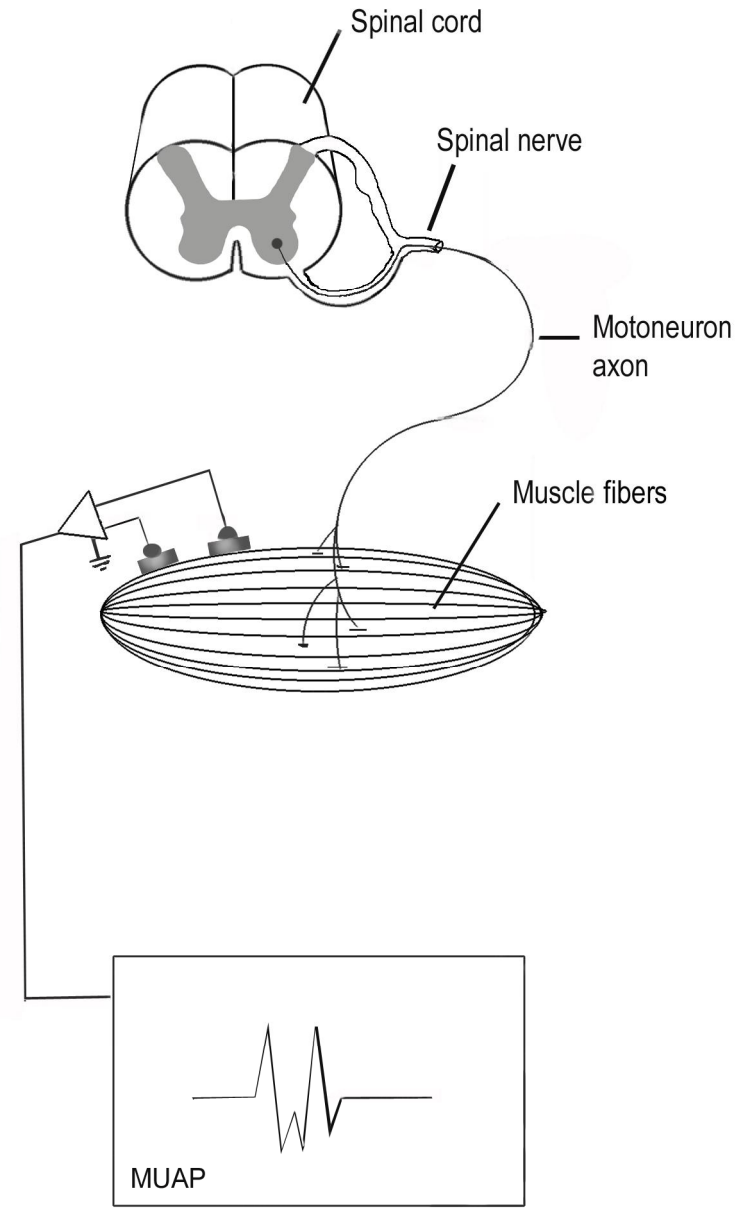

Figure 6. Motoneuron and motor unit action potential (MUAP).

The surface EMG can be represented in amplitude and frequency. When EMG is analysed in clinical neurophysiology, a high-pass filter (optimal at 20 or 25 Hz, depending on the muscle, van Boxtel 2001) is applied to minimize artefacts. During depth of anaesthesia monitoring high-pass filter is set typically below 1 Hz; for example, the high-pass filter is set at 0.8 Hz in Entropy monitoring.

Frequency content of the recorded EMG signal is a prominent feature in EMG analysis. The APs travelling in fast-twitch fibres have a higher frequency content, because of the higher conduction velocity. To simplify, the frequency content of EMG is analysed the same way as the frequency content of EEG, e.g. using FFT. Surface EMG has a frequency range from 0 to > 200 Hz, or even higher (van Boxtel 2001, Kamata et al 2011). The skeletal muscle EMG has several more or less distinct spectral components: a 0-5 Hz component thought to reflect a common drive to motor units, a 10 Hz component reflecting motor unit firing and physiological tremor, a 20-30 Hz component (EMG beta rhythm), and a 35-60 Hz component (Piper rhythm) (McAuley et al. 1997). The use of a notch filter in EMG analysis is controversial, because considerable spectral energy is present in the 50-60 Hz range.

Like the EEG, the EMG registering is prone to many confounding factors. Among these factors is the low-pass filtering effect of the tissues between the electrodes and the muscle fibres. The blood flow can affect the characteristics of the surface-recorded signal (by low-pass filtering).

2.3.2. Anatomy and physiology of upper facial muscles

There are several fundamental differences in the anatomy and physiology of frontal (and orbicularis oculi) and temporal muscles. Frontal and orbicularis oculi muscles are considered expressive muscles, and the temporal muscle is a masticatory muscle. The innervation to frontal and orbicularis oculi muscles arises from the seventh cranial (facial) nerve, and the innervation to the temporal muscle arises from the mandibular division of the fifth cranial (trigeminal) nerve (Kahle and Frotscher 2010).

The frontal and orbicularis oculi muscles are attached only to the skin, not to bony structures. The temporal muscle originates in the scalp above the temporal

region and inserts into the upper part of the jaw. The overall cross-sectional appearance of facial muscle fibres resembles that of striated limb muscles (Schwarting et al. 1982). The percentage of type I (slow) fibres varies from 43 to 87% in the frontal muscle and from 0.5 to 23% in orbicularis oculi muscle (Johnson et al. 1973). The temporal muscle has a higher (73 to 87%) percentage of type I fibres. The different proportion of slow fibres is explained by the different actions of these muscles. The frontal muscle acts by tonic contraction during information processing tasks, orbicularis oculi muscle is involved in blinking, and the temporal muscle is involved in the act of raising the mandible and closing the jaws.

Frontalis muscle is electrically silent unless involved in an emotional response or a cognitive task. It lacks muscle spindles (neuromuscular feedback system that allows muscles to determine how stretched the muscle tissue is) and has a low innervation ratio (van Boxtel et al. 1983). Force of contraction in frontal muscle is controlled primarily by the firing rate modulation of the facial nerve (instead of the recruitment process) (Fuglevand et al. 1993).

There is a high incidence of power spectra with a firing rate peak in the frontal muscle, although there is variability between individuals. The temporal muscle has power spectra without a firing rate peak. This finding is related to the different functions of these muscles. In other words, the spontaneous activity of the frontal muscle requires tonic discharge of one or only few motor units, and the function of the temporalis muscle requires strong and dynamic contractions (van Boxtel and Jessurun 1993).

2.3.3. EMG, general anaesthesia and depth of anaesthesia monitoring

As mentioned earlier, the activation of frontal muscle EMG (FEMG) during general anaesthesia has been suggested to be a useful indicator of impending arousal, or a sign of nociception. The relationship between EMG, NMBAs, the actual depth of anaesthesia, and the depth of anaesthesia monitoring has been studied for over 40 years. These studies have been conducted in different clinical settings and using different study drugs, and the results have not been uniform. At least three entities, although reviewed here separately, but having similarities, must be considered when interpreting the results of these studies:

1. NMBAs and actual depth of anaesthesia
2. NMBAs, EMG and numerical values of depth of anaesthesia monitors
3. Reversal of NMB, EMG and depth of anaesthesia monitoring

2.3.3.1. NMBAs and actual depth of anaesthesia

Since the introduction of curare to the clinical practice, controversy has existed over whether NMBAs possess anaesthetic properties (Whitacre and Fisher 1945). It was clinically noted that less anaesthetic was needed in the presence of curare, but this notion was countered by the accusation that the inability to move masked the inadequate anaesthesia. In 1979, Forbes and co-workers conducted a study, where pancuronium reduced the halothane requirement in man. They used halothane as an anaesthetic, and the halothane requirement was defined using the MAC concept (MAC is the minimum alveolar concentration needed to suppress movement response to skin incision in 50% of the subjects). The use of pancuronium reduced the MAC of halothane by 25%, from 0.73 ± 0.04 to 0.55 ± 0.04% (mean ± SEM). The authors concluded that their results were caused by the abolished muscle spindle afferent input to the reticular activating system, resulting in deafferentation of the cortex (afferent muscle spindle theory) (Forbes et al. 1979). In other studies, results along the same line were obtained (Schwartz et al. 1992, Lanier et al. 1994). Also conflicting results have been published (Fahey et al. 1989). In this well

conducted study, the effects of three different NMBAs (atracurium, vecuronium, pancuronium) were studied. None of these NMBAs had any effect on the halothane requirement in humans.

This subject has been studied also in the era of EEG-based depth of anaesthesia monitoring. In the first study, the effect of different degrees of NMB on BIS values was studied during deep (BIS 40 ± 5 (mean ± SD)) propofol anaesthesia. The study was conducted without nociceptive stimuli, and also the EMG activity was absent already before administration of NMBA. The increasing level of NMB did not have any effect on the BIS values. Thus, the study did not support the afferent muscle spindle theory (Greif et al. 2002). In another study conducted during propofol-remifentanil anaesthesia in the absence of surgical stimuli, no effect of NMB on BIS could be seen (Vasella et al. 2005). The effect of NMB on the BIS values during sevoflurane anaesthesia was studied in another study, this time with and without noxious stimulation (Ekman et al. 2007). In the absence of nociceptive stimuli, the BIS values were not affected by the NMB. In the presence of nociceptive stimuli, the BIS values were affected by the degree of NMB. In all the above mentioned studies, only the numerical values of BIS were studied and the raw EEG signal was not analysed.

To summarize, there is conflicting information about the effect of NMBAs on the depth of anaesthesia. During deep anaesthesia and in the absence of noxious stimuli, no evidence of the afferent muscle spindle theory has been found. However, the afferent input from the peripheral proprioceptors may produce a weak central effect, detectable only during light levels of anaesthesia and/or in the presence of noxious stimuli.

2.3.3.2. NMBAs, EMG and numerical values of depth of anaesthesia monitors

The question about the effect of EMG activity on the depth of anaesthesia monitors seems easier to answer. The first case report about the elevated BIS values caused by EMG was published in 2000 (Bruhn et al. 2000). Since then, numerous other reports have been published. These include the BIS values declining in fully awake persons during neuromuscular block (Messner et al. 2003), overestimation of BIS

values during sedation in intensive care (Vivien et al. 2003), and overestimation of BIS values intraoperatively (Baldesi et al. 2004).

To conclude, it has been shown that BIS is affected by EMG activity. In most cases, the BIS values have returned to "normal" values after administration of NMBA. The increase in the numerical values of BIS caused by EMG and the return to baseline values after NMBA are explained by the overlapping power spectra of EEG and EMG (van Boxtel 2001, Kamata et al. 2011). In all likelihood, all EEG-based depth of anaesthesia monitors are similarly affected by the contaminating effect of EMG.

2.3.3.3. NMB reversal, EMG and depth of anaesthesia monitoring

At the end of operation, if the muscle strength has not returned spontaneously, the NMB is reversed pharmacologically. The NMB is reversed most often with neostigmine, an anticholinesterase. The NMB induced by rocuronium or vecuronium can also be antagonized with sugammadex, a new cyclodextrin-derived drug, which is capable of reversing even profound NMB in three minutes (Lee et al. 2009). The controversy surrounding the reversal of NMB, EMG and the depth of anaesthesia monitors is analogue to the chapters 2.3.3.1. and 2.3.3.2.: Is the actual depth of anaesthesia affected by the return of proprioceptive input from the periphery? Is the change in the numerical values of depth of anaesthesia monitors caused by EMG? Do the reversal agents possess properties affecting the actual depth of anaesthesia?

Reversal of NMB with neostigmine during light propofol-remifentanil anaesthesia (BIS 55) produced a rise in BIS values by 7 (7.5) (mean (SD)) BIS units, and an increase in BIS EMG from 27.7 (1.3) to 31.2 (5.3) dB. Three patients presented unexpected movement and coughing; one of the patients remembered this after operation. As neostigmine does not cross the normal blood-brain barrier (BBB), the authors concluded that their results support the afferent muscle spindle theory (Vasella et al. 2005). In another study, the effect of reversal of NMB with sugammadex on BIS and Entropy values during deep (BIS 32) propofol-remifentanil anaesthesia was studied. No effect of NMB reversal with sugammadex on the numerical values of BIS and Entropy was detected (Illman et al. 2010).

In a study comparing the effects of sugammadex and neostigmine on the numerical values of BIS, it was shown that both reversal agents increased BIS values, and that the increase in BIS values was associated with increased EMG activity (Dahaba et al. 2012).

In two studies regarding NMB reversal with sugammadex, it was discovered that the administration of sugammadex during propofol anaesthesia (combined with an opioid) produced an elevation in BIS values, sucking, grimacing, moving or coughing in 18 out of 88 and in 30/157 patients, respectively (Sparr et al. 2007, Pühringer et al. 2008). The authors speculated that the findings were supportive of the afferent muscle spindle theory. However, these studies were not designed to study the behaviour of BIS, nor was BIS used in all patients. Recently, Inoue and co-workers reported a recovery from general anaesthesia with sevoflurane after a neurosurgical operation that was achieved by the administration of neostigmine, causing central cholinergic activation (Inoue et al. 2010). Physostigmine, an anticholinesterase that is able to cross BBB, has been reported to antagonize the hypnotic effect of propofol (Meuret et al. 2000, Xie et al. 2011). On the other hand, the hypnotic effect of sevoflurane can be only partly antagonized by physostigmine (Plourde et al. 2003).

The relationship between reversal of NMB and depth of anaesthesia is not clear. Based on the current literature, it can be concluded that during deep levels of anaesthesia, the return of afferent proprioceptive input does not influence the depth of anaesthesia. It is possible that arousal caused by the return of muscle strength is very small, only quantifiable at light levels of anaesthesia. Also, if the BBB is not intact, the anticholinesterases will cause central cholinergic activation, resulting in a return of consciousness.

2.4. EEG-based depth of anaesthesia monitoring

The first to describe (animal) EEG was a Liverpool-based physician Richard Caton in 1875 (Caton 1875). The pioneer in the studies on human EEG was Hans Berger, a German psychiatrist, who systematically described human EEG (and the effect of chloroform on human EEG) in his publications (Berger 1929, Berger 1931). Less than ten years later after Berger's discovery of human EEG, it was reported that EEG is sensitive to anaesthetic agents, and that EEG could be used as a tool for measuring anaesthetic depth (Gibbs et al. 1937). Already in 1950, Bickford introduced an EEG-derived parameter (total EEG power) to control depth of anaesthesia (Bickford 1950).

Improvements in EEG monitoring technology and comprehensive understanding of EEG during the following 60 years have made real-time EEG monitoring during general anaesthesia possible. Monitoring the anaesthetic drug effect with EEG is what is nowadays called "depth of anaesthesia monitoring". Several commercial methods for EEG-based depth of anaesthesia monitoring are available.

The EEG-based depth of anaesthesia monitors have been proven to reliably show the depth of hypnosis with isoflurane, sevoflurane, desflurane, thiopental and propofol (Sebel et al. 1997, Vakkuri et al. 2004). All these anaesthetics act on the CNS via gamma amino butyric acid receptor type A ($GABA_A$). It must be kept in mind that the EEG-based depth of anaesthesia monitors cannot separate consciousness from unconsciousness when agents, whose action is mediated mainly via glutamate NMDA receptor (ketamine, nitrous oxide as a sole agent, or xenon) are used.

2.4.1. Classic EEG parameters

Since Bickford's suggestion to use EEG parameters to control the depth of anaesthesia, several time and frequency domain based parameters have been suggested for this purpose.

Zero crossing frequency (ZXF) is a parameter that describes how many times the EEG curve crosses the baseline in a predetermined time period. Basically, the ZXF

is high in awake subjects and decreases with increasing depth of anaesthesia. The ZXF was shown to correlate with the dose of propofol (Herregods et al. 1989). The method has its limitations, of course: not all waves in the EEG cross the baseline, EEG consists of many frequencies therefore the ZXF changes from epoch to epoch.

Spectral edge frequency (SEF), peak power frequency, median frequency, relative delta power, and many other univariate descriptors have also been studied intensively. To summarize, they all have serious limitations and have had only limited success in adequately describing depth of anaesthesia (Hudson et al. 1983, Rampil and Matteo 1987). They are mentioned here only for historical reasons.

2.4.2. Burst suppression

Burst suppression, an EEG pattern not present in physiologic sleep, can be used as a tool for monitoring depth of anaesthesia. Burst suppression is a sign of moderate to deep anaesthesia.

When treating patients with refractory status epilepticus in the intensive care, the goal is to produce EEG burst suppression by barbiturate anaesthesia. It has also been suggested that burst suppression could be used in patients with a history of intraoperative awareness to ensure adequate depth of anaesthesia (Brundidge et al. 1994). The disadvantage of using burst suppression as a goal for adequate depth of anaesthesia is that the patient may be exposed to overdosing of anaesthetic agents.

2.4.3. Bispectral Index Scale (BIS)

The first commercially successful, and the most widely adopted EEG-based depth of anaesthesia monitor is the Bispectral Index Scale (BIS). The BIS monitoring has been available since October 1996 (Johansen and Sebel 2000). Since then, a number of revisions have been made to the BIS monitor, mainly to improve artefact rejection and detection of suppression-like EEG tracings.

The development of BIS and the algorithm used by BIS are described by Rampil in his comprehensive review on EEG, signal processing and BIS (Rampil 1998). The BIS utilizes a sensor placed on the forehead of the patient (Figure 7). The BIS sensor (since 2001) has four electrodes, and presumably it records and analyses one-

channel EEG (Johansen 2006). For bilateral monitoring, the manufacturer also has a sensor with six electrodes.

The algorithm used in BIS monitoring is partly non-public, but some aspects of BIS monitoring have been published (Rampil 1998, Morimoto et al. 2004). In short, BIS utilizes time domain (burst suppression ratio, QUAZI suppression), frequency domain (beta ratio), and high-order spectral (bispectral) subparameters (SynchFastSlow). Thus, the combination of these four subparameters produces a single number, which decreases with decreasing level of consciousness, during physiological sleep and in cases of pathological EEG. However, the value of the bispectral subparameter has been questioned; the same information could be obtained by using a simpler and faster method, the power spectrum (Miller et al. 2004, Schneider et al. 2004).

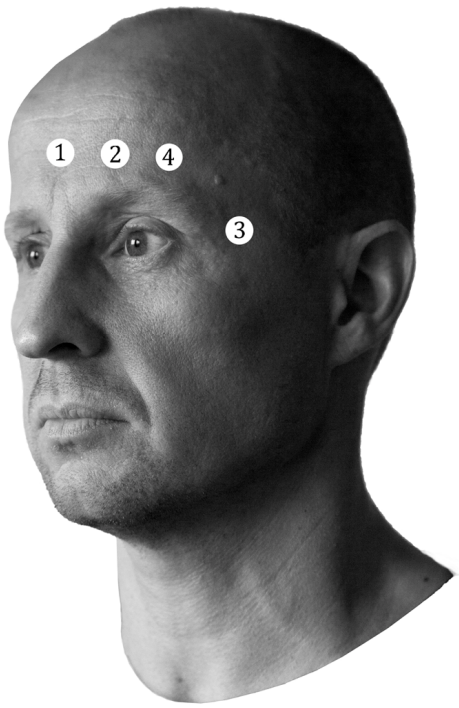

Figure 7. The montage used in BIS and Entropy monitoring. The BIS sensor has four electrodes (1-4), and the Entropy sensor has three electrodes (1-3). The corresponding electrode positions in international 10-20 electrode placement system are (approximately) as follows: 1 = F_{pz}, 2 = F_{p1}, 3 = $F_{9,}$ 4 = AF_7.

To summarize, BIS monitor yields a single number, BIS, on the monitor screen. The BIS scale is from 100 (awake) to 0 (suppressed EEG). The range recommended during surgical anaesthesia by the manufacturer is 40-60. On the BIS monitor, also bars indicating signal quality index (SQI) and the amount of EMG activity are visible, as well as a 20-second piece of the EEG signal. The bandwidth in BIS analysis is 1-47 Hz for EEG and 70-110 Hz for EMG.

In high-risk patients, the BIS monitoring has been reported to reduce the risk of awareness and recall during anaesthesia by approximately 80 % (Myles et al. 2004, Ekman et al. 2004). However, more recent studies have not proven that BIS-guided anaesthesia results in reduced incidence of awareness when compared to end-tidal anaesthetic gas (ETAG)-guided anaesthesia (Avidan et al. 2008, Avidan et al. 2011). In addition to measuring the hypnotic component of anaesthesia, BIS monitoring has been reported to result in faster wake-up (Gan et al. 1997), allow shorter stay in post anaesthesia care unit (White et al. 2004), reduce the consumption of anaesthetics (Wong et al. 2002, Luginbühl et al. 2003), and reduce the incidence of postoperative nausea and vomiting (Nelskylä et al. 2001, Luginbühl et al. 2003).

It has also been reported that unnecessarily deep level of anaesthesia (cumulative time with BIS < 45) is an independent risk factor for postoperative mortality (Monk et al. 2005, Lindholm et al. 2009, Leslie et al. 2010a, Kertai et al. 2010). Based on these studies, it has been suggested that BIS monitoring should be used to avoid unnecessarily deep levels of anaesthesia. However, these studies were hampered by some methodological weaknesses, and later studies, in which the methodology has been better, have not confirmed this finding (Kertai et al. 2011, Lindholm et al. 2011).

2.4.4. Time-frequency balanced spectral entropy (Entropy)

In this part of the review, the word “Entropy” is used to describe a specific method for EEG-based depth of anaesthesia monitoring, time-frequency balanced spectral entropy. The general concept of entropy (disorder, irregularity, randomness of a system) is omitted from this review.

The Entropy monitor was introduced in 2004. The algorithm of Entropy has been fully published (Viertiö-Oja et al. 2004). In the Entropy monitoring, a three-electrode (two recording electrodes and a ground electrode) sensor collecting one-channel EEG is attached to the forehead of the patient (Figure 7). The two recording electrodes are placed so that the first electrode is on the frontal muscle, recording EEG from the frontal pole, and the second electrode is on the orbicularis oculi and temporal muscles, recording EEG from frontal and temporal lobes, including basal forebrain and mesial temporal cortex.

In the calculation of Entropy, EEG epochs of varying lengths (1.92 to 45 seconds) are analysed. The length of the epochs varies: the lower the frequencies of the signal are, the longer is the analysed epoch. In Entropy monitoring, the power spectrum of the epoch is normalized so that the sum of normalized power spectrum at the desired frequency range equals one. Then a mathematical function, Shannon’s function, is applied, yielding Entropy value between 0 and 1. The frequency bands of interest in Entropy monitoring are 0.8-32 Hz and 0.8-47 Hz. In the concept of Entropy, the frequencies from 0.8 to 32 Hz are thought to reflect EEG activity, and the frequencies from 32 to 47 Hz are thought to reflect EMG activity.

Entropy monitoring yields three parameters: State Entropy (SE), Response Entropy (RE), and Burst Suppression Ratio (BSR). The SE values are calculated from the 0.8-32 Hz frequency band, the RE values are calculated from the 0.8-47 frequency band. The BSR values are calculated by another method, described in detail by Särkelä et al (Särkelä et al. 2002). The dimensionless scales for SE and RE are 0-91 and 0-100, respectively. The scale for BSR is 0-100 (%).

Rather than being considered an artefact, an effort has been made to utilize EMG activity in Entropy monitoring. As the appearance of upper facial EMG activity can be a sign of nociception or impending arousal (Paloheimo et al. 1989, Dutton et al.

1998), the difference between RE and SE (RE-SE) has been suggested to be an indicator of insufficient analgesia. This hypothesis has been supported by some studies (Wheeler et al. 2005, Takamatsu et al. 2006), but also disputed by others (Valjus et al. 2006, Hans et al. 2006).

Like BIS, Entropy has been shown to be a valid indicator of the hypnotic effect of propofol, thiopental, isoflurane, sevoflurane, and desflurane (Vakkuri et al. 2004). It has also been shown to reduce the consumption of anaesthetics, and to enhance recovery (Vakkuri et al. 2005).

2.4.5. Other EEG-based depth of anaesthesia monitors

Several other methods for EEG-based depth of anaesthesia monitoring are commercially available. These include (among others) Narcotrend (MonitorTechnik, Bad Bramstedt, Germany), SNAP II (Everest Biomedical Instruments Company, Chesterfield, MO, USA), Patient State Index (Hospira Inc., Lake Forest, IL, USA), Cerebral State Monitor (utilizes EEG and auditory evoked potentials, Danmeter, Odense, Denmark), and Index of Consciousness (IoC, Morpheus Medical, Barcelona, Spain).

2.4.6. Causes for misleading values in monitoring

2.4.6.1. Artefacts

As mentioned earlier, the first commercially available and most widely adopted EEG-based depth of anaesthesia monitor is BIS. Therefore it is natural that most reports on artefacts causing misleading index values have been reports on BIS. These artefacts can be either physiological (originating from other organs than the brain) or non-physiological (originating from external devices). Some examples of the physiological artefacts causing misleading index values are EMG and electrocardiogram (ECG) (Hemmerling et al. 2008). Among the non-physiologic artefacts causing misleading index values are cardiac pacing devices (Gallagher 1999, Vretzakis et al. 2005), cardiopulmonary bypass machine (Tewari and Skinner 2007), warming blankets (Guignard and Chauvin 2000, Hemmerling and Fortier

2002, Zanner et al. 2006), endoscopic shavers (Hemmerling and Migneault 2002), electromagnetic systems (Hemmerling and Desrosiers 2003), and EMG tracheal tube (Sloan 2007).

Owing to the fact that the electrodes are placed on the forehead, EMG is a potential artefact in the EEG-based depth of anaesthesia monitoring. The frequencies of EEG and EMG overlap in a very wide frequency range (van Boxtel 2001, Goncharova et al. 2003, Kamata et al. 2011); therefore it is not possible to separate EMG from EEG by band-pass filtering. In this review, the relationship between EMG activity and EEG-based depth of anaesthesia monitoring has been discussed in detail in chapter 2.3.3.

2.4.6.2. Changes in EEG caused by anaesthetics and opioids

Although burst suppression is not an artefact, it has been reported to cause misleadingly high values in Entropy monitoring (Hart et al. 2009). As mentioned earlier, burst suppression is a sign of a very deep anaesthesia. If the depth of anaesthesia monitor confuses EEG burst suppression with the EEG of the awake state, the patient may be exposed to overdosing of anaesthetic agents.

Opioids, when given in large amounts, cause a shift to lower frequencies in EEG. The slowing of EEG is interpreted by depth of anaesthesia monitors as a deeper level of the anaesthesia. Thus, awareness during anaesthesia has been reported, when excess amounts of opioids have been administered without a sufficient amount of anaesthetics (Vassiliadis et al. 2007).

2.4.6.3. Changes in EEG not caused by anaesthetics

Low-voltage EEG is a genetically inherited condition, where the amplitude of EEG is no more than 20 μV in all head regions. It is estimated that the incidence of low-voltage EEG is 5-10% of the normal population. The incidence of low-voltage EEG is an age-related phenomenon; low-voltage EEG in children is never physiologic, but with increasing age, EEG may become lower in amplitude. The brain function of the persons with low-voltage EEG is normal. The person with low-voltage EEG has been reported to have low BIS values when totally awake (Schnider et al. 1998). In

order to avoid misinterpretation in these patients, it is recommended that normal depth of anaesthesia values should be confirmed before induction of anaesthesia.

Finally, it must be kept in mind that the changes in EEG caused by deepening anaesthesia (a shift from higher frequencies to lower frequencies) can also be caused by other causes. These causes include severe hypoglycaemia, post-ictal state after electroconvulsive therapy, brain death, cardiac arrest, cerebral ischemia, hypothermia, Alzheimer's disease, cerebral palsy and severe brain injury. A comprehensive review, describing the effects of these highly exceptional states on the BIS monitoring, has been published (Dahaba 2005). In addition to this excellent review, it should be emphasized that all EEG-based depth of anaesthesia monitors are equally affected by these states, *i.e.* not all changes in EEG are caused by anaesthetics.

To avoid over- and underdosing of anaesthetic agents caused by misleading values by the depth of anaesthesia monitors, several authorities have recommended that anaesthesiologist relying on the numerical values of the EEG-based depth of anaesthesia monitors should also be capable of interpreting the raw EEG signal on the anaesthesia monitor (Jäntti 2005, Barnard et al. 2007, Bennett et al. 2009, Mashour et al. 2011, Bottros et al. 2011).

3. Aims of the study

The aim of this study was to study the different arousal reactions during general anaesthesia, and the effect of these arousal reactions on the behaviour of two clinically used depth of anaesthesia monitors, Entropy and BIS. The specific aims were:

1. To study Entropy's numerical values during intubation and skin incision, and to investigate the impact of EMG arousal on these values, during propofol-nitrous oxide or propofol-nitrous oxide-remifentanil anaesthesia (I).
2. To study the one-channel EEG recorded by the Entropy for signs of visual EMG and EEG arousal, and to investigate the effect of different arousal types on the numerical values of Entropy, during sevoflurane-nitrous anaesthesia with or without rocuronium (II).
3. To compare the effects of neostigmine or sugammadex on the numerical values of Entropy and BIS, during propofol-remifentanil-rocuronium anaesthesia (III).
4. To study whether the intubation-associated EMG arousal can be visually detected on the anaesthesia monitor (IV).

4. Patients and methods

Table 1. Summary of the studies.

Study	n	Groups	Randomization	Double-blind
I	15 16	Propofol-N_2O Propofol-N_2O-remifentanil	No	No
II	19 19	Sevoflurane-N_2O Sevoflurane-N_2O-rocuronium	No	No
III	15 15	Sugammadex Neostigmine	Yes	Yes
IV	17 17	Rocuronium 0.6 mg/kg Rocuronium 1.2 mg/kg	Yes	Yes

4.1. Patients

The patients had to fulfil similar, specific inclusion and exclusion criteria in studies I-IV. The inclusion criteria were: female patients undergoing elective surgery, ASA physical status 1 or 2, BMI < 30 (< 28 in studies I and II), age 18-65 (18-60 in studies I and II) years. The exclusion criteria were: disease or injury affecting the central nervous system, alcohol or drug abuse, allergy to any of the drugs used during the study.

4.2. Methods

4.2.1. Study designs

Study I was designed to investigate Entropy's numerical values during nociceptive stimuli (endotracheal intubation and skin incision), and to analyse the one-channel EEG recorded by the Entropy strip in both time and frequency domain for signs of EMG arousal. The patients received either only propofol (bolus + continuous infusion), or propofol (bolus + continuous infusion) and remifentanil-TCI at 4 ng/ml.

Study II was designed to analyse the one-channel EEG recorded by Entropy to detect EEG patterns, EMG and artefacts during skin incision. Also, the numerical values of Entropy were analysed. The patients were anaesthetized with sevoflurane-nitrous oxide or sevoflurane-nitrous oxide-rocuronium. EEG arousal was classified as beta (increase of over 8 Hz activity and decrease of under 4 Hz activity with typical beta pattern) or delta (increase of under 4 Hz activity with characteristic rhythmic delta pattern, and decrease of over 8 Hz activity).

Study III assessed the clinically observed phenomenon that antagonism of NMB causes a rise in the numerical values of BIS and Entropy. After operation, during light propofol-remifentanil anaesthesia, NMB was antagonized with sugammadex or neostigmine. During the following five-minute study period, the numerical values of BIS, BIS EMG and Entropy were recorded on a laptop computer, as well as the biosignal recorded by the Entropy strip. The Entropy biosignal was studied off-line both in time and frequency domain to discover whether the rise in the numerical values of BIS and Entropy caused by NMB reversal is an electroencephalographic or electromyographic phenomenon.

Study IV was designed to investigate if EMG arousal can be visually detected in the raw EEG signal on the anaesthesia monitor. The patients received either 0.6 or 1.2 mg/kg of rocuronium to facilitate endotracheal intubation. The raw biosignals of BIS and Entropy were recorded in full HD resolution with a video camera, and analysed off-line. Also the one-channel EEG recorded by the Entropy was analysed off-line to discover the incidence of EMG arousal using two doses of rocuronium.

4.2.2. Premedication and monitoring

In studies I-IV, all patients received 10 mg oral diazepam approximately 60 minutes before induction of anaesthesia. In the OR, an intravenous infusion of isotonic saline was started to all patients. Monitoring included 3-lead ECG, pulse oximetry (SpO_2), non-invasive blood pressure, and neuromuscular transmission (NMT). Fractions of inspiratory (Fi) and end-tidal (Et) concentrations of oxygen, carbon dioxide, nitrous oxide (Studies I and II) and sevoflurane (Studies I and II) were also monitored. Gas measurements were made using a connecting piece at the face mask.

4.2.3. Acquisition and analysis of EEG

Studies I-IV: The one-channel EEG was collected with Entropy module. Entropy monitoring started before induction of anaesthesia and continued uninterrupted until the end of the study. A disposable electrode strip for Entropy measurement was used. The forehead skin was degreased using 70% isopropanol and the skin was allowed to dry. The strip was positioned according to manufacturer's guidelines so that it acquired the biosignal from two electrodes of the strip: one frontally in the midline, 2 cm above the eyebrows, and the other 2 cm laterally from the outer canthus of the eye. The first electrode was on the frontal muscle, recording EEG from frontal poles, and the second electrode was on the orbicularis oculi and temporal muscles, recording EEG from frontal and temporal lobes, including basal forebrain and mesial temporal cortex. The EEG was collected with an Entropy Module of the S/5™ Anaesthesia Monitor with a sampling rate of 400 Hz. Entropy monitoring utilizes high and low pass filters of 0.5 and 118 Hz (-3 dB; 60 dB/decade), respectively. Power line artefact at 50 Hz was not filtered.

Studies I-IV: The analysis of one-channel EEG included visual inspection, as well as calculation of power spectra and spectrograms. The power spectra and spectrograms were produced with Somnologica™ sleep analysis program (Medcare Flaga, Reykjavik, Iceland).

4.2.4. Data collection

Studies I-IV: the numerical data of all recorded parameters were downloaded and stored on a laptop computer with S5 Collect software (GE Healthcare) at 5-second intervals. The same software was used continuously in the collection of one-channel EEG.

4.3. Statistical analysis

4.3.1. Sample size estimation

Study I: Power calculation was based on the hypothesis that surgery would cause mean RE-SE differences of 7.0 and 2.0 units (SD 4.5 units) in patients receiving propofol and propofol-remifentanil, respectively. The study was designed to have power of 80% to detect statistical significance, assuming two-sided α-level of 0.05. To meet the criteria of power calculation, 14 patients per group were needed.

Study II: To test whether RE-SE difference is lower when NMBAs are used, the study was designed to have power of 80% to detect statistical significance in RE-SE difference between groups with and without rocuronium, assuming two-sided α-level of 0.05, with nociception-associated mean RE-SE differences of 2 and 5.5 units (SD 3 units) between groups, respectively. To meet the criteria of power calculation, 13 patients per group were needed.

Study III: Based on our preliminary data, we assumed a mean maximal change of 15 (SD 7.5) SE units in patients receiving sugammadex, and 7 (SD 7.5) SE units after administration of neostigmine. We calculated the sample size using the level of statistical significance as $\alpha = 0.05$ and $\beta = 0.2$. Fifteen patients were needed in both groups to test our hypothesis.

Study IV: Based on the results of Study II, we assumed that intubation would cause EMG arousal in 55% of the patients receiving 0.6 mg/kg of rocuronium. Based on earlier results by others, we assumed intubation-associated EMG arousal in 10% of the patients receiving 1.2 mg/kg of rocuronium. We calculated the sample size using the level of statistical significance as $\alpha = 0.05$ and $\beta = 0.2$. Fifteen

patients were needed in both groups to test our hypothesis. To allow for dropouts, we decided to increase the group size to seventeen.

4.3.2. Data analysis

Studies I-IV: All statistical analyses were performed using SPSS for Windows (SPSS Inc., Chicago, IL) software (version 16.0 in Studies I and II, version 17.0 in Studies III and IV). In all the studies, $P<0.05$ was considered statistically significant. The continuous variables were presented as means with SD. The categorical variables were presented as absolute frequencies.

Study I: One-way analysis of variance (ANOVA), followed by t-tests were used for parametric data, and Mann-Whitney and chi-square tests for non-parametric comparisons. Pearson correlation analysis was used to compare the change of HR to the change of RE-SE difference at endotracheal intubation.

Study II: One-way analysis of variance (ANOVA), followed by t-tests were performed for parametric data, or by chi-square tests for non-parametric comparisons.

Study III: Demographic data were analysed with unpaired t-test. ASA classification and the type of surgery were analysed with Fisher's exact test.

Study IV: Demographic data were analysed with unpaired t-test. ASA classification was analysed with Fisher's exact test. The inter-rater agreements with BIS and Entropy were measured by calculating Cohen's kappa coefficient.

4.4. Ethical statement

The studies were approved by the ethics committee of the Tampere University Hospital (I-IV) and by the National Agency for Medicines (I-III). The studies were conducted in accordance with the Declaration of Helsinki. The studies III and IV were also approved by the European Clinical Trials Database (EudraCT) and registered at ClinicalTrials.gov. All patients gave preoperative written informed consent.

The studies were supported solely by departmental sources of Department of Anaesthesia, Tampere University Hospital.

5. Results

Study	N	Group	Age	Weight	Height
I	15	Propofol-N_2O	39 (11)	62 (8)	166 (5)
	16	Propofol-N_2O-remifentanil	32 (10)	61 (9)	165 (6)
II	19	Sevoflurane-N_2O	33 (9)	66 (13)	167 (7)
	19	Sevoflurane-N_2O-rocuronium	31 (6)	63 (10)	167 (6)
III	15	Sugammadex	42 (9)	67 (11)	166 (4)
	15	Neostigmine	45 (13)	65 (8)	165 (7)
IV	17	Rocuronium 0.6 mg/kg	40 (12)	69 (6)	167 (6)
	17	Rocuronium 1.2 mg/kg	46 (12)	65 (8)	163 (5)

Table 2. Demographic data in studies I-IV, presented as mean (SD).

5.1. Effect of EMG arousal on Entropy

The numerical values of Entropy (RE, SE, and RE-SE) increased and EMG arousal was detected during intubation during propofol-nitrous oxide and propofol-nitrous oxide-remifentanil anaesthesia. In most cases, elevated RE values were followed by elevated SE values. During skin incision, EMG arousal was detected only in patients not receiving remifentanil.

In the patients with increasing Entropy values, spectral analysis of the Entropy biosignal revealed increased EMG activity starting from low (<20 Hz) frequency area until the highest measurable frequency values.

Owing to their overlapping power spectra, the contribution of EMG and EEG cannot be accurately separated with frequency analysis in the range of 10 - 40 Hz.

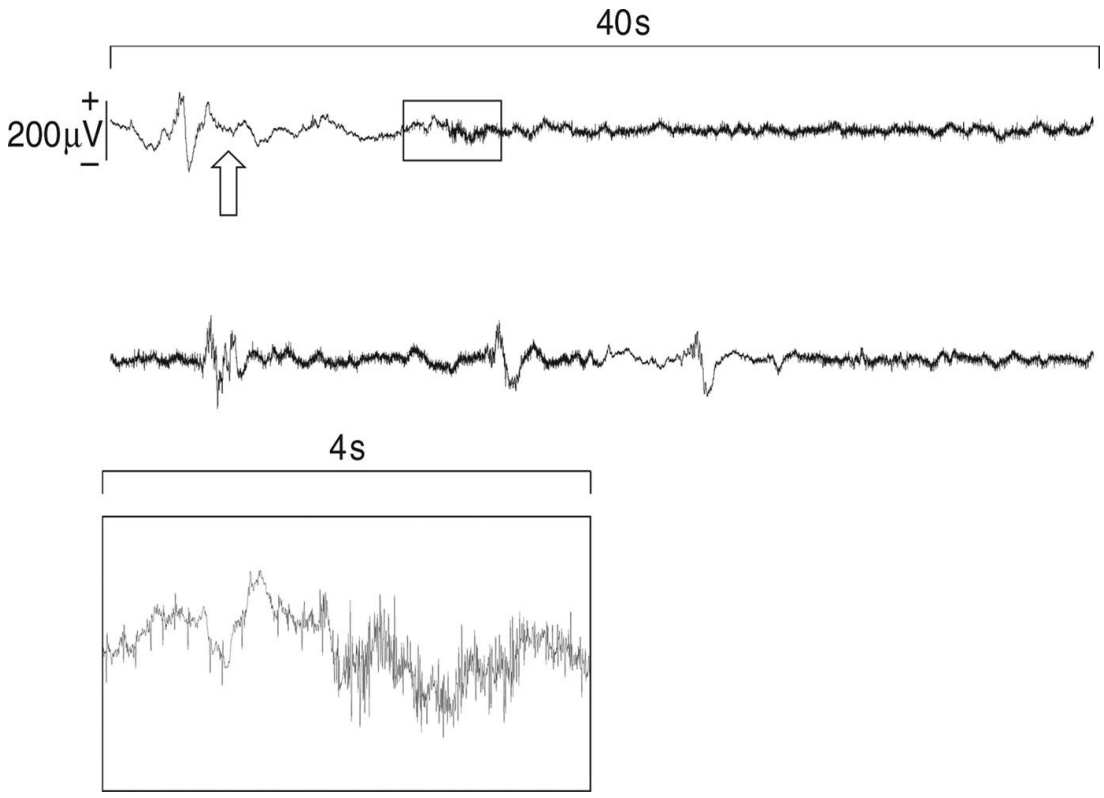

Figure 8. Two successive 40-second samples of EEG, showing the development of EMG arousal after intubation (arrow upward) during EEG burst suppression. Even the motor unit action potential can be seen (box below EEG samples) (reproduced with the kind permission of Oxford University Press).

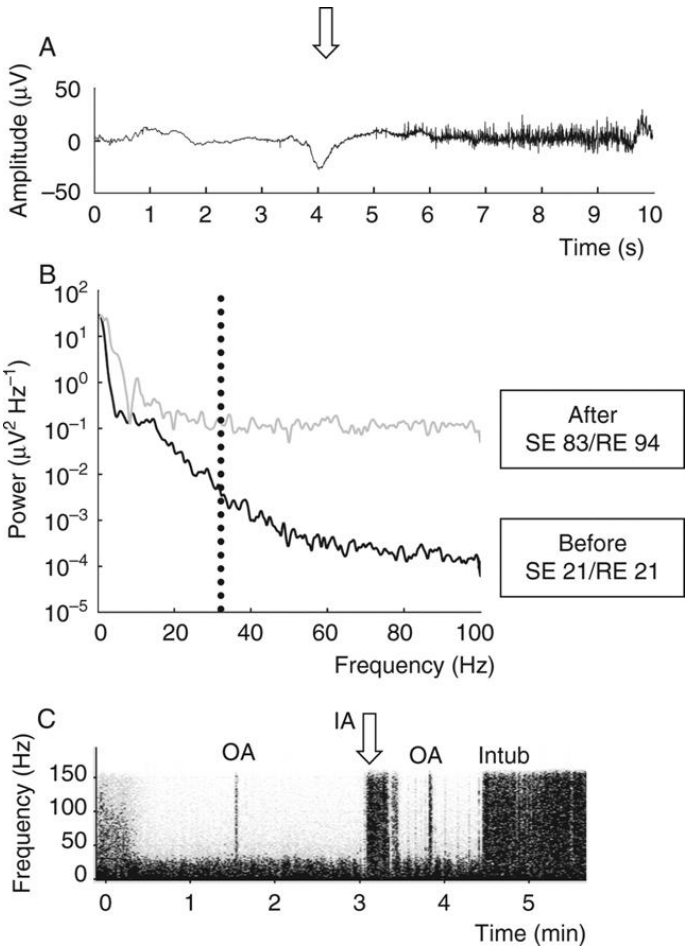

Figure 9. The contaminating effect of EMG arousal on one-channel EEG and the EEG power spectrum after laryngoscopy (arrow downward) and attempted intubation in one patient without remifentanil (reproduced with the kind permission of Oxford University Press).

5.2. Skin incision and Entropy

5.2.1. EEG arousal during skin incision

EEG arousal appeared in 17/19 and 15/19 patients (NS), with and without rocuronium, respectively. Beta arousal (n = 30) increased SE and RE. Delta arousal (n = 2) decreased both SE and RE.

5.2.2. EMG arousal during skin incision

EMG arousal appeared in 0/19 and 13/19 patients ($P<0.01$) with and without rocuronium, respectively. A significant rise in RE-SE was only seen in patients without rocuronium. EMG arousal was abolished by rocuronium at TOF level 0/4.

5.3. Comparison of sugammadex and neostigmine

Reversal of NMB with sugammadex produced a strong response (SE > 80) in five patients, a weak response (SE 60-80) in four patients, and no response (SE < 60) in six patients. Administration of neostigmine produced a strong response in five patients, a weak response in one patient, and no response in nine patients (NS). The rise in SE values was most likely caused by increased electromyographic (EMG) activity. The administration of sugammadex or neostigmine appeared to have only minimal effect on EEG.

5.4. Visual detection of EMG arousal

Strong EMG arousal (rise in SE value > 60) was detected visually by the anaesthesiologist in 2/3 patients with both BIS and Entropy. The clinical neurophysiologist detected strong EMG arousal in 2/3 patients with BIS and 3/3 patients with Entropy.

When also the weaker EMG arousals were taken into account, a total of 13 EMG arousals were found. The anaesthesiologist could detect EMG on the monitor in 7/13 (specificity 54%) patients with BIS, and in 4/13 (31%) patients with Entropy. The clinical neurophysiologist detected EMG in 4/13 (31%) patients with BIS, and in 5/13 (38%) with Entropy. In addition, a total of 23 false positive EMG detections were made by the observers. Inter-rater agreement was 0.12 (slight agreement) with BIS, and 0.72 (substantial agreement) with Entropy.

6. Discussion

6.1. Effect of EMG arousal on Entropy

The effect of EMG arousal on Entropy monitoring was studied in Study I. It was shown that laryngoscopy and endotracheal intubation increase the numerical values of SE, RE and RE-SE difference. The RE-SE difference is, at best, a short-lasting indicator of nociception in patients anaesthetised with propofol, nitrous oxide and remifentanil without neuromuscular blocking agents. When interpreted incorrectly, the intubation-associated increase in SE may indicate awareness, even during burst suppression anaesthesia. The increase in SE is caused by the overlapping power spectra of EMG and EEG in the frequency range of <20-50 Hz. The patient may be exposed to overdosing of anaesthetic agents, if the EMG arousal leads to increasing the amount of anaesthetic administered to the patient. In other words, adequate anti-nociceptive medication or effective NMB are preferable in avoiding and treating high Entropy values caused by EMG arousal. The finding that EMG activity starts at frequencies < 20 Hz is contradictory to the description of Entropy algorithm (Viertiö-Oja et al. 2004). Earlier studies have reported contradictory results about the usefulness of RE-SE difference as an indicator of nociception (Wheeler et al. 2005, Valjus et al. 2006). This study offers an electrophysiologic explanation to the different findings reported earlier.

6.2. Skin incision and Entropy

6.2.1. EEG arousal during skin incision

In study II, EEG arousal was seen in 32 out of 38 patients. Rocuronium did not have an effect on EEG arousal. Most EEG arousals were beta arousals (n = 30). In two patients, delta arousal was seen. EEG delta arousal has also been called paradoxical arousal (Bischoff et al. 1993) or reverse arousal (Brazier 1964).

EEG beta arousal leads to increasing the anaesthetic given to the patient. EEG delta arousal and the following decrease in Entropy's SE value, if interpreted incorrectly, may lead to decreasing the concentration of the anaesthetic, increasing the possibility of awareness during anaesthesia.

The neurophysiologic mechanisms of arousal during anaesthesia are relatively poorly known. Kellaway (Kellaway 1990) has suggested that they are probably closely related to arousal mechanisms of physiological sleep, which can also produce different types of EEG patterns, especially in children. Studies done with cats indicate that slow EEG delta activity may be related to the activation of reticular formation of the brainstem (Kaada et al. 1967). It has also been suggested that delta arousal occurs when patient is exposed to surgical stimuli during inadequate analgesia (Kiyama and Takeda 1997, Morimoto et al. 2005).

6.2.2. EMG arousal during skin incision

In Study II, EMG arousal caused an increase in Entropy's numerical values. EMG arousal was abolished by rocuronium at TOF 0/4. These findings are in line with the results of Study I. The increase in Entropy values was caused by the EMG contamination of EEG. The EMG activity is present at frequencies below 20 Hz, therefore the respective power spectra of EEG and EMG overlap significantly in the frequency range of 20-50 Hz. EMG arousal may lead to overdosing of anaesthetic agents.

Owing to their overlapping power spectra, the contribution of EEG and EMG cannot be accurately separated by Entropy. Visually it may be impossible to

distinguish between beta activity and EMG in sleep or anaesthesia recordings, as EMG generated at a distance from the recording electrodes loses its sharp, spiky appearance. I hypothesize that this finding explains the earlier reports where NMBAs have been shown to have an effect on numerical values of the depth of anaesthesia monitors (Vivien et al. 2003, Messner et al. 2003, Hans et al. 2006). Entropy monitoring is susceptible to the use of rocuronium, limiting the usefulness of RE and RE-SE in detecting nociception in the presence of strong neuromuscular blockade.

6.3. Comparison of sugammadex and neostigmine

The study III showed that reversal of NMB by sugammadex or neostigmine during light propofol-remifentanil anaesthesia increased the numerical values of BIS and Entropy in some patients. This finding is in line with some of the earlier studies (Vasella et al. 2005), but somewhat different from the findings of Illman et al. (Illman et al. 2010).

The anaesthetics in our study were similar to these earlier studies, but the analysis of the BIS and Entropy values was different. In the study by Vasella et al., the BIS values were averaged over one minute and only the numerical values of BIS and BIS EMG were analysed. In our study, we used the maximal values, and we also analysed the actual biosignal recorded by the Entropy strip. I hypothesize that our method is more accurate in detecting the cause to the increased numerical values of BIS and Entropy. In the study by Illman et al. (Illman et al. 2010), the patients' depth of anaesthesia was deeper, offering an explanation why our results were different.

A similarly conducted study was published at the same time as our study, and yielded almost identical results and conclusions (Dahaba et al. 2012). This study studied only the numerical values of BIS, without any actual EEG analysis.

In our study, the one-channel EEG recorded by the Entropy strip was analysed by all available means, to discover the electrophysiologic phenomena behind increasing index values. The increased BIS and Entropy values were most likely caused by the EMG contamination of EEG. However, small changes in EEG activity may not be visible during strong EMG activity.

6.4. Visual detection of EMG arousal

Several authors have proposed that anaesthesiologists using depth of anaesthesia monitors should interpret the biosignal on the anaesthesia monitor, instead of relying on the numerical values of EEG-based depth of anaesthesia monitors (Jäntti 2005, Barnard et al. 2007, Bennett et al. 2009, Hart et al. 2009). Our study was designed to provide an answer to this suggestion.

Our results showed that strong EMG arousal was reasonably well detected (in two out of three cases) by the experienced analysts. The weaker EMG arousals were more difficult to see visually both with BIS (sensitivity 54 and 31 %, specificity 57 and 57 % by the anaesthesiologist and the clinical neurophysiologist, respectively) and with Entropy (sensitivity 31 and 38 %, specificity 85 and 90 % by the anaesthesiologist and clinical neurophysiologist, respectively). In addition, kappa coefficient was calculated to measure the inter-rater agreement. When BIS biosignal was analysed, kappa coefficient was 0.12 (slight agreement). In the analysis of Entropy biosignal, kappa coefficient was 0.72 (substantial agreement). These results showed that EMG arousal cannot be reliably detected visually on the anaesthesia monitor. Therefore, technological improvements are warranted in the depth of anaesthesia monitors.

6.5. Strengths and weaknesses of the studies

The reasons for this thesis were the observations in clinical practice, when anaesthesiologist using Entropy or BIS monitoring encounters strangely behaving numerical values of these monitors. All the studies in this thesis were designed to investigate the changes in the original one-channel EEG in connection with changes in the numerical values of Entropy and BIS. To our knowledge, these studies were the first to analyse the one-channel EEG in detail. The previous reports had only described the behaviour of the numerical values of BIS and Entropy. In all four studies, the sample size was based on power analysis calculation to enrol an ideal number of patients.

The four studies in this thesis were intended to answer following clinical problems: 1) to what extent Entropy's numerical values are affected by EMG

contamination of EEG, 2) how Entropy's numerical values are affected by different types of EEG arousal, and by EMG arousal with and without NMBA, 3) why the numerical values of BIS and Entropy increase after reversal of NMB, and 4) if it is possible to detect intubation-associated EMG arousal visually on the screen of the anaesthesia monitor. Complete or partial answers to these four questions were found, and hopefully anaesthesiologists using BIS and Entropy are able to react in a more adequate way to the changes caused by different arousal reactions to the numerical values of BIS and Entropy.

First, in the absence of adequate nociception or effective neuromuscular block during propofol anaesthesia, EMG arousal can increase the numerical values of Entropy to awake values. The response to this increase will not necessarily be to increase the amount of anaesthetic to the patient, but to administer opioid and/or NMBA.

Second, EEG beta arousal can be effectively abolished by increasing the amount of anaesthetic given to the patient. However, EEG delta arousal should not be treated by decreasing the amount of anaesthetic, as this may expose the patient to awareness during anaesthesia. EEG delta arousal can be visually detected on the anaesthesia monitor, so correct displaying and interpretation of the raw biosignal is necessary.

Third, an increase in the numerical values of BIS and Entropy after reversal of NMB with sugammadex or neostigmine may be seen. This phenomenon is most likely an EMG phenomenon, not an EEG phenomenon.

Fourth, strong EMG arousal can be visually detected on the anaesthesia monitor. A weaker EMG arousal may remain undetected; therefore, technological improvements are still needed to today's monitoring technologies.

The weaknesses of the studies are as follows:

Studies I-IV: Only one-channel EEG was recorded and analyzed. As EEG and EMG arousals often occur simultaneously, more than one channel should be recorded to more accurately detect them.

Studies I and II: The patient groups were not blinded, so using placebo would have resulted in a better quality of the study.

Study III: Lack of placebo group.

Studies III and IV: An obvious limitation of these studies is that the collection and analysis of the biosignal was possible only from the Entropy sensor, not from

the BIS sensor. Owing to the contralateral placement of the sensors, it is possible that they may register information differently. For example, if the activated motor unit is directly under one of the sensors, the motor unit potential will affect one sensor more strongly than the other sensor. Therefore, the biosignal recorded by the Entropy sensor may de different from the biosignal recorded by the BIS sensor.

6.6. Clinical aspects and future perspectives

The EEG-based depth of anaesthesia monitoring became commercially available in the 1990s. In addition to measuring the hypnotic component of anaesthesia, they have been reported to reduce the risk of awareness and recall during anaesthesia (Myles et al. 2004, Ekman et al. 2004), although not all studies have confirmed this finding (Avidan et al. 2008, Avidan et al. 2011). In addition, the use of depth of anaesthesia monitoring may reduce the consumption of anaesthetics and enhance the recovery from anaesthesia (Vakkuri et al. 2005).

Several contaminating artefacts have been shown to cause misleading values of the EEG-based depth of anaesthesia monitors. These artefacts can be either physiological (originating from other organs than the brain) or non-physiological (originating from external devices). Some examples of the physiological artefacts are EMG and patient's own ECG (Hemmerling et al. 2008). Among the non-physiologic artefacts are cardiac pacing devices (Gallagher 1999, Vretzakis et al. 2005), cardiopulmonary bypass machine (Tewari and Skinner 2007), warming blankets (Guignard et al. 2000, Hemmerling et al. 2002, Zanner et al. 2006), endoscopic shavers (Hemmerling and Migneault 2002), electromagnetic systems (Hemmerling and Desrosiers 2003), and EMG tracheal tube (Sloan 2007). Also, as studied in Study II, EEG arousals can cause changes in the numerical values of depth of anaesthesia monitors, without an actual change in the depth of anaesthesia.

Owing to the confounding effects of these artefacts, the EEG-based depth of anaesthesia monitoring, as used today, is far from perfect. Situation could be improved by technological advances: the resolution of the monitors could be enhanced; more than one EEG channel could be registered; the depth of anaesthesia monitoring could include a third dimension to indicate EEG arousal; the power spectrum and/or spectrogram could be added to the display of the monitor, offering

relevant information about the origin of the cause for misleading numerical values. Also the filtering process in the monitoring systems could be improved in order to minimize the effect of non-physiological artefacts. The concentrations of anaesthetics could be fed into the depth of anaesthesia monitors, not necessarily to form closed-loop drug administration, but to help decision making; if the concentrations of the anaesthetic drugs remain unaltered, perhaps it could guide anaesthesiologist's thinking towards the idea "Hmm, is there an external reason for strangely behaving numerical values of my index?".

7. Conclusions

On the basis of these studies, the following conclusions can be drawn:

1. The power spectra of EEG and EMG overlap significantly; therefore they cannot be accurately separated with frequency analysis in the range of 20 - 50 Hz. The contaminating effect of EMG causes a rise in the numerical values of Entropy.

2. Skin incision may cause both EEG and EMG arousals during sevoflurane-nitrous oxide anaesthesia. EEG beta and delta arousals have opposite effects on the Entropy's numerical values. EMG arousal was abolished by rocuronium at TOF level 0/4.

3. The reversal of NMB by sugammadex or neostigmine may increase BIS and Entropy values during light propofol-remifentanil anaesthesia. This rise is most likely caused by increased EMG activity, not by changes in EEG.

4. Unlike many EEG phenomena, EMG arousal cannot be reliably detected visually on the anaesthesia monitor, even by a very experienced person. Therefore, technological improvements to today's monitoring technology are warranted.

5. When an anaesthesiologist is using EEG-based depth of anaesthesia monitoring, it is of importance to display the original biosignal, and to have the necessary skills to interpret it correctly.

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Facial muscle activity, Response Entropy, and State Entropy indices during noxious stimuli in propofol–nitrous oxide or propofol–nitrous oxide–remifentanil anaesthesia without neuromuscular block

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Background. Entropy™ is an anaesthetic EEG monitoring method, calculating two numerical parameters: State Entropy (SE, range 0–91) and Response Entropy (RE, range 0–100). Low Entropy numbers indicate unconsciousness. SE uses the frequency range 0.8–32 Hz, representing predominantly the EEG activity. RE is calculated at 0.8–47 Hz, consisting of both EEG and facial EMG. RE–SE difference (RE−SE) can indicate EMG, reflecting nociception. We studied RE−SE and EMG in patients anaesthetized without neuromuscular blockers.

Methods. Thirty-one women were studied in propofol–nitrous oxide (P) or propofol–nitrous oxide–remifentanil (PR) anaesthesia. Target SE value was 40–60. RE−SE was measured before and after endotracheal intubation, and before and after the commencement of surgery. The spectral content of the signal was analysed off-line. Appearance of EMG on EEG was verified visually.

Results. RE, SE, and RE−SE increased during intubation in both groups. Elevated RE was followed by increased SE values in most cases. In these patients, spectral analysis of the signal revealed increased activity starting from low (<20 Hz) frequency area up to the highest measured frequencies. This was associated with appearance of EMG in raw signal. No spectral alterations or EMG were seen in patients with stable Entropy values.

Conclusions. Increased RE is followed by increased SE at nociceptive stimuli in patients not receiving neuromuscular blockers. Owing to their overlapping power spectra, the contribution of EMG and EEG cannot be accurately separated with frequency analysis in the range of 10–40 Hz.

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EEG is the method of choice in measuring the hypnotic component of anaesthesia. During the last decade, several measures have been introduced for this purpose. The most widely adopted EEG measure of anaesthetic drug effect is Bispectral Index (BIS™ monitor, Aspect Medical Systems, Newton, MA, USA).[1] BIS utilizes a sensor placed in the forehead and temple of the patient to collect EEG. Although the approach is easy to use for anaesthetists, the placement is prone to facial EMG contamination,[2] which is shown to represent impending arousal or nociception,[3] even during deep hypnosis with propofol.[4] Therefore, a single-number index like BIS can never tell with certainty the impact of EMG on the information received from the analysed signal.

To at least partly overcome the problem described above, another EEG monitoring device, the M-ENTROPY™ module (GE Healthcare, Helsinki, Finland), was introduced.[5] The M-ENTROPY™ module calculates the characteristics of the upper facial biosignal with an analysis of time–frequency balanced spectral entropy, taking into account the special

[†]*Declaration of interest*. Professor Yli-Hankala is a paid consultant for GE Healthcare Finland.

characteristics of suppressed EEG signal. The resulting index of EEG and EMG activity is called Entropy, which has been shown to be a valid indicator of the hypnotic effect of propofol, thiopental, isoflurane, sevoflurane, and desflurane.[6]

Entropy consists of two parameters: State Entropy (SE) and Response Entropy (RE). SE is computed over the frequency range from 0.8 to 32 Hz, which represents the EEG-dominant part of the frequency spectrum. Therefore, SE reflects the cortical state of the patient. RE is computed over the frequency range from 0.8 to 47 Hz, covering both the EEG-dominant and the EMG-dominant areas of the spectrum. Consequently, RE−SE difference serves at least partly as an indicator of upper facial EMG activation.[5]

The RE and SE are both calculated with 5 s intervals from the preceding 1.92 and 15 s segments of EEG, respectively, and the new values are shown on the screen and output from the monitor.

The appearance of upper facial EMG indicates that the patient is responding to an external stimulus,[7] which is usually nociceptive. Therefore, RE−SE difference may indicate nociception or inadequate anaesthesia, an assumption supported by one recently published article,[8] but disputed by another.[9]

The present study was designed to prospectively investigate RE, SE, RE−SE difference, and upper facial EMG during propofol–nitrous oxide or propofol–nitrous oxide–remifentanil anaesthesia in patients without neuromuscular blocking agent (NMBA) medication (i) before and after intubation and (ii) before and after beginning of laparoscopic surgery. The primary aim of the study was to evaluate the behaviour of RE, SE, and RE−SE difference between the groups. Secondary aims were to compare the Entropy indices between intubation and surgery, to study the impact of visually verified EMG on the indices, and to make comparisons between heart rate (HR) and RE−SE difference. As remifentanil is a very potent opioid, we hypothesized that smaller increase in RE, and therefore, smaller RE−SE difference would be seen in patients receiving remifentanil as an adjuvant of their propofol–nitrous oxide anaesthesia. We also hypothesized that EMG would react more precisely than EEG to nociceptive stimuli, and that changes of RE−SE difference would associate with alterations in HR. To our knowledge, this is the first clinical study where the appearance of EMG is verified visually both from the original biosignal and from its spectral presentation, and compared with the behaviour of the Entropy parameters.

Methods

Patients

This study followed the design of a prospective clinical study. The local Ethics Committee and Finnish National Agency for Medicines approved the study protocol. All patients gave their written informed consent. Inclusion criteria were the following: patients undergoing elective laparoscopic gynaecological surgery (expected duration >30 min) between ages 18 and 60 yr, and ASA physical status I or II. Patients were excluded if they had a disease or injury affecting the central nervous system, alcohol or drug abuse, or BMI >28. All patients fasted overnight before surgery. A total of 33 patients were enrolled.

Electroencephalogram acquisition

The forehead biosignal was collected with a disposable electrode strip (Entropy Sensor, GE Healthcare) for Entropy measurement. After degreasing of the forehead skin using isopropanol 70%, the strip was positioned as recommended by the manufacturer. The signal was acquired from two electrodes of the strip: one frontally in the midline, 2 cm above the eyebrows, and the other 2 cm laterally from the outer canthus of the left eye. The first electrode is on the frontal muscle, the second on the orbicularis oculi and temporal muscles. Entropy was collected with an M-ENTROPY^{TM} module of the S/5^{TM} Anesthesia Monitor (GE Healthcare). The sampling rate was 400 Hz. High- and low-pass filters of 0.5 and 118 Hz (−3 dB; 10 dB per decade), respectively, were applied. Power line artifact was not filtered. All the monitored values were collected on a laptop computer.

Anaesthesia and study protocol

RE, SE, and vital signs were collected under two anaesthetic regimens, both of which included premedication with diazepam 10 mg p.o. An i.v. route was established for all patients and an infusion of isotonic saline was started. Intermittent non-invasive arterial pressure was recorded every 5 min. Electrocardiogram, inspired fractions and end-tidal concentrations of anaesthetic gases and CO_2, and peripheral oxygen saturation were continuously monitored with the Datex-Ohmeda S/5^{TM} Anesthesia Monitor.

Entropy monitoring started before induction of anaesthesia and continued uninterrupted until the end of the study. Seventeen patients were anaesthetized with propofol 3 mg kg^{-1} i.v., followed by manually controlled ventilation of nitrous oxide 67% in oxygen via face mask. Endotracheal intubation was performed, as gently as possible, 150 s later. If intubation difficulties were met, mask ventilation was re-started and another intubation attempt was done 1–3 min later. If the second attempt was unsuccessful, rocuronium was given and the patient was discarded from the study. After securing the airway, controlled mechanical ventilation was started with a fresh flow of 6 litre min^{-1} (67% nitrous oxide in oxygen), and propofol infusion was started. The infusion rate of propofol was adjusted to keep the Entropy parameters between 40 and 60, the target being 50.

Sixteen patients were anaesthetized the same way as described above, but target-controlled infusion (TCI,

Asena^{TM} PK, Alaris Medical Systems, Basingstoke, UK) of remifentanil was added to the anaesthetic regimen. Remifentanil was infused with the estimated effect-site concentration (Ce) of 4.0 ng ml^{-1} from the beginning of anaesthetic induction (the pharmacokinetic model of Minto and colleagues)[10] until the end of the study. Laryngoscopy for endotracheal intubation was initiated after reaching the remifentanil Ce of 4.0 ng ml^{-1}.

After endotracheal intubation, patients were not touched or otherwise disturbed for 5 min to discover the magnitude of RE−SE difference, and the presence or absence of EMG, during anaesthesia without surgery. After 5 min, the patient was prepared for operation and permission to start laparoscopy was granted. A propofol bolus of 50 mg was given as a rescue medication if the Entropy values exceeded 60, and repeated 90 s later, if needed. The study was completed 1 min after setting the first laparoscopy trochar. Thereafter, the administration of nitrous oxide was discontinued and patient's lungs were ventilated with air/oxygen. Fentanyl (the propofol group) and rocuronium were given according to clinical needs.

Analyses of the biosignal

RE and SE values were analysed off-line as a mean of 15 s (three consecutive readings) at the following time points: awake, 90 s after anaesthetic induction, 30 s before intubation, 30 s after intubation, after a 5 min equilibrium period, 60 s before skin incision, 30 s after skin incision, 30 s after setting of the needle of Veress, 30 s after beginning of gas insufflation, at the end of gas insufflation, and 30 s after setting of the first laparoscopy trochar. RE−SE was calculated by subtracting the SE value from the corresponding RE value.

Spectrogram, that is, a presentation of the spectral content of a biosignal, was produced with Somnologica^{TM} sleep analysis program (Medcare Flaga, Reykjavik, Iceland). Power spectra of consecutive 1.0 s samples of the signal are calculated and presented vertically along *y*-axis, plotted against time in *x*-axis. The density (i.e. 'darkness') of spectrogram reveals the amount of activity at respective frequency. Thus, spectrogram presents the same information as successive power spectra, but in a compressed form. Power line artifact is seen in spectrogram as a sharp activity band at 50 or 60 Hz, and ECG or EOG artifacts are typically located at rather low frequency range. Therefore, EMG is virtually the only artifact that is displayed over a wide frequency range.

Both the raw biosignal and a spectrogram at the time points of interest were inspected visually off-line, without knowledge of the behaviour of the Entropy indices, by an experienced clinical neurophysiologist (V.J.), to judge the presence or absence of EMG. Later on, the traces and classifications were analysed jointly by all authors, to ensure the agreement of the detections. To demonstrate the effect of EMG on the EEG spectrum, spectral analyses before and after intubation or commencement of surgery were drawn in four patients. In analyses, a window of 15 s was used.

All patients were interviewed during the first postoperative day, regarding their possible anaesthesia and surgery-related memories and intubation-associated sequelae.

Statistical methods

The study was designed to have a power of 80% to detect statistical significance, assuming two-sided α-level of 0.05, with surgery-associated mean RE−SE differences of 7.0 and 2.0 units (SD 4.5 units) between the propofol and the propofol−remifentanil groups, respectively. The power calculation was based on the previous unpublished Entropy data of our own. To meet the criteria of power calculation, 14 patients per group were needed. All statistical analyses were performed using SPSS for Windows software (version 16.0, SPSS, Chicago, IL, USA). One-way analysis of variance followed by *t*-tests was used for parametric data, and Mann–Whitney and χ^2 tests were used for non-parametric comparisons, where appropriate. Pearson's correlation analysis was used to compare the change of HR with that of RE−SE difference at endotracheal intubation. $P<0.05$ was considered statistically significant.

Results

Two enrolled patients, both receiving propofol−nitrous oxide without remifentanil, were excluded because of problems in laryngoscopy and intubation. All others were successfully intubated with one or two attempts. Therefore, 15 patients in the propofol−nitrous oxide group and 16 patients in the propofol−nitrous oxide−remifentanil group were studied. Patient characteristics did not differ between the groups. The mean ages of patients not receiving remifentanil and those with remifentanil were 39 *vs* 32 yr, mean weight was 62 *vs* 61 kg, and mean height was 166 *vs* 165 cm, respectively.

The RE or SE values did not differ between the groups along the study. The RE−SE difference showed significant between-group difference awake and from skin incision to the end of the study. Awake, the mean of propofol−nitrous oxide group was 1.22 units higher ($P<0.042$). Therefore, the groups were baseline-corrected by subtracting 1.22 units from all means in the propofol−nitrous oxide group. After such correction, the only detected between-group difference was after setting the first laparoscopy trochar. The behaviour of RE, SE, baseline-corrected RE−SE difference, and HR in both groups is presented in Figure 1.

The SE and RE values increased more commonly after intubation than after skin incision (Table 1). RE increased ≥10 units in 27 events. This increase in RE values was rapidly followed by ≥10 units increase of SE in 21/27 cases, thereby decreasing the calculated RE−SE difference.

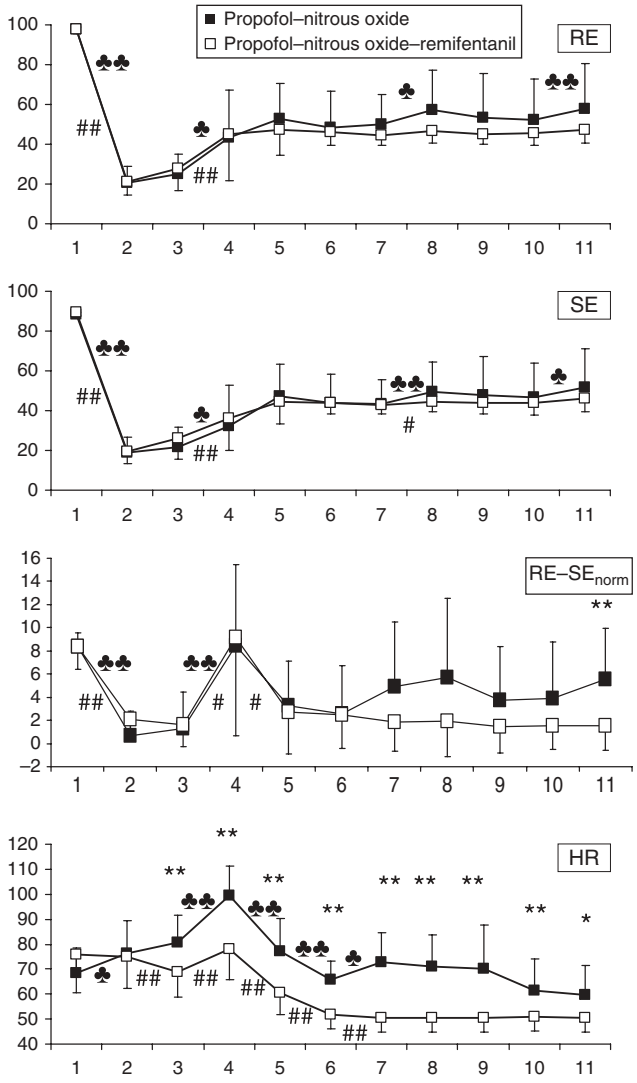

Fig 1 The behaviour of RE, SE, baseline-corrected RE−SE, and HR [mean (SD)] during the study in patients receiving propofol–nitrous oxide or propofol−nitrous oxide−remifentanil anaesthesia. 1, awake; 2, 90 s after anaesthetic induction; 3, 30 s before intubation; 4, 30 s after intubation; 5, after a 5 min equilibrium period; 6, 60 s before skin incision; 7, 30 s after skin incision; 8, 30 s after setting of the needle of Veress; 9, 30 s after beginning of gas insufflation; 10, at the end of gas insufflation; 11, 30 s after setting of the first laparoscopy trochar. ♣$P<0.05$, ♣♣$P<0.01$ within the propofol–nitrous oxide group, respectively. #$P<0.05$, ##$P<0.01$, and *$P<0.05$, **$P<0.01$ within the propofol–nitrous oxide–remifentanil group, and between the groups, respectively.

When all blindly analysed episodes of interventions were pooled together, the EMG was present more frequently in recordings of patients in the propofol group (79 EMG findings in 165 episodes) than in the propofol–remifentanil group (33 findings in 176 episodes). Incidence of EMG in both groups and the association between EMG and Entropy RE−SE difference are given in Table 2. In some patients, EMG changed the power spectrum of the biosignal from 15 Hz up to ∼150 Hz, that is, to the highest detectable frequencies. The presence of EMG in the raw biosignal of an example patient, and its effect on power spectrum, Entropy values, and spectrogram, is depicted in Figure 2.

Figure 3 presents the spectrograms from the whole study period in two patients, one in the propofol group and another in the propofol−remifentanil group. In some patients, the EMG was seen on the top of suppressed EEG signal in association with noxious stimulus (Fig. 4).

The mean time intervals from induction of anaesthesia to intubation were 161 and 168 s for groups without and with remifentanil, respectively (NS). The same figures for intervals from anaesthetic induction to skin incision were 29 and 32 min, respectively (NS).

HR was similar in both groups, awake and 90 s after induction of anaesthesia. From intubation to the end of the study period, HR was higher in patients without remifentanil (Fig. 1). The correlation between the change of HR and that of RE−SE difference at endotracheal intubation was poor: $r=0.179$ ($P=0.336$).

Rescue medication due to elevated SE values was needed 18 times in 12 patients (nine in the propofol group and three in the propofol–remifentanil group). None of the patients, however, had recall, sore throat, or other complaints in the postoperative interview.

Discussion

The first finding in our study was that RE, SE, and RE−SE difference increased in both groups during laryngoscopy and endotracheal intubation, along with continuous EMG activity in the biosignal, in spite of remifentanil (4.0 ng ml^{-1}) in one group. The second finding was that the intubation-associated increase in RE−SE difference was only transient, because the increase in RE was often

Table 1 Number of patients with small (<10), moderate (10 to ≤30) or large (>30 units) change in SE or RE values at intubation or skin incision. The mean of three consecutive index values before intubation or skin incision is subtracted from that of three consecutive values 1 min after the event. *$P=0.006$, **$P=0.001$ for SE and RE change values, respectively, between intubation and skin incision (two-tailed Mann–Whitney test)

Magnitude of change in index values	Intubation*, **				Incision			
	Propofol		Propofol–remifentanil		Propofol		Propofol–remifentanil	
	SE	RE	SE	RE	SE	RE	SE	RE
<10 units	7	4	8	7	9	9	16	15
10 to ≤30 units	4	7	6	5	5	5	0	1
>30 units	4	4	2	4	1	1	0	0
Σ	15	15	16	16	15	15	16	16

Table 2 The occurrence of visible EMG in EEG signal along the course of study in patients receiving propofol–nitrous oxide or propofol–remifentanil–nitrous oxide anaesthesia, and the association of EMG with RE–SE difference

Time point	EMG present/absent (*n*)			RE–SE [mean (SD)]		
	Propofol	Propofol–remifentanil	*P*-value (Fisher's exact test)	EMG present	EMG absent	*P*-value (*t*-test)
Awake	15/0	16/0	1.0	8.96 (1.70)		
Induction+90 s	5/10	4/12	0.704	2.44 (2.35)	1.72 (1.83)	0.43
Before intubation	1/14	0/16	0.484	12 (0)	1.73 (1.86)	<0.001
After intubation	15/0	13/3	0.226	9.96 (7.6)	0.67 (0.33)	<0.001
Steady state	4/11	0/16	0.043	8 (1.63)	2.93 (3.6)	0.001
Before skin incision	2/13	0/16	0.226	12 (1.41)	2.52 (2.73)	0.027
After skin incision	6/9	0/16	0.007	12.17 (3.49)	1.96 (2.13)	<0.001
Needle of Veress	6/9	0/16	0.007	13 (6.48)	2.28 (3.01)	0.009
Start of gas insufflation	7/8	0/16	0.002	7.57 (5.16)	1.83 (2.44)	0.025
End of gas insufflation	8/7	0/16	0.001	8.38 (4.5)	1.52 (1.81)	0.003
Laparoscopy trochar	10/5	0/16	<0.001	9.1 (2.92)	1.62 (1.96)	<0.001

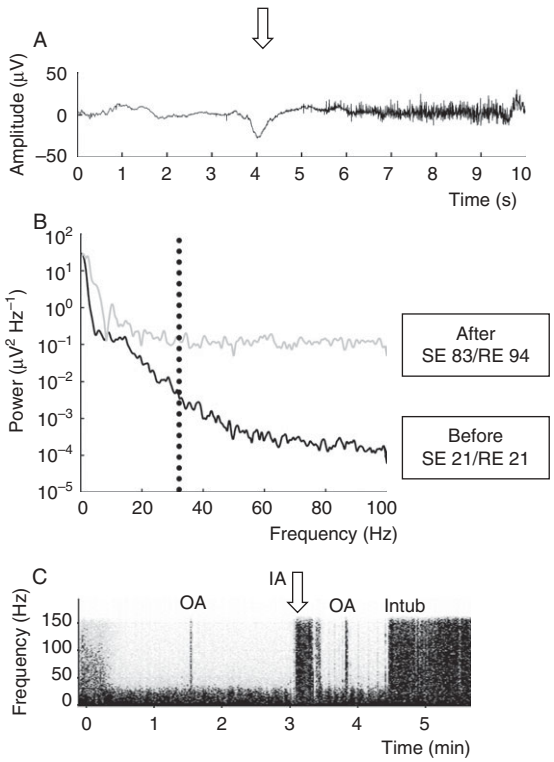

Fig 2 (A) The appearance of EMG activity in EEG signal after laryngoscopy (arrow downward) and attempted intubation in a patient not receiving remifentanil. EEG signal remains suppressed, despite strong EMG contamination. (B) Power spectrum of the EEG signal before (black line) and after (grey line) laryngoscopy in the same situation as in (A). EMG activity changes the spectrum after laryngoscopy. The spectrum with EMG impact starts to change already below 20 Hz. Dotted vertical line represents the 32 Hz frequency, which is used in Entropy calculation to differentiate EEG activity (<32 Hz) from EMG activity (>32 Hz). In Entropy calculation, low SE value increases rapidly after appearance of EMG, because the power at <32 Hz area increases. (C) EEG spectrogram (frequency *vs* time) of the same patient as in (A) and (B). Fast activity disappears in the beginning of anaesthesia (0–30 s). Continuous activity below 30 Hz is merely EEG. Placement of oropharyngeal airway (OA) at 1 min 40 s elicits short EMG response, shown as a vertical bar up to 150 Hz. Laryngoscopy and attempted intubation (IA) at arrow is associated with longer EMG response. Replacement of oropharyngeal airway at 3 min 50 s, and successful intubation (Intub) at 4 min 30 s. Long-lasting EMG activity ensues.

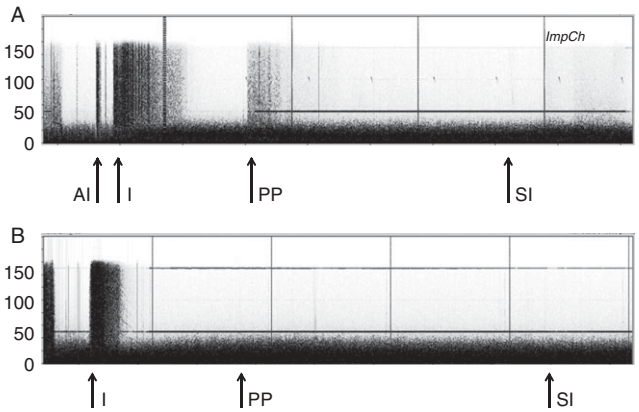

Fig 3 EEG spectrograms presenting the whole study periods in two patients: (A) without and (B) with remifentanil infusion. Fast activity disappears in the beginning of anaesthesia. EEG activity is seen in both recordings as a continuous activity below 30 Hz. EMG contamination is seen as vertical bars up to 150 Hz. AI, attempted intubation; I, intubation; PP, patient positioning; SI, skin incision. Laryngoscopy and intubation are associated with strong EMG activity in both recordings. Thereafter, no EMG is seen in (B), that is, the patient receiving remifentanil. In (A), both noxious and non-noxious stimuli (like positioning the patient) elicit EMG activity. Horizontal bars at 50 and 150 Hz are power line (50 Hz) artifacts and its harmonic (150 Hz). Vertical bars (ImpCh) indicate automatic Entropy sensor impedance checks every 10 min.

rapidly followed by an increase in SE. These findings suggest that RE−SE difference cannot be used as a long-lasting, reliable indicator of nociception. Although regularly detected in the initial phase of stimulation, RE−SE difference soon disappears due to increasing SE.

The small, though statistically significant, difference in RE−SE awake was most likely due to random factors,[11] because no abnormal EEG was seen in visual evaluation. However, this difference in RE−SE awake was taken into account by normalizing the groups in the way described in Results. After baseline correction according to the awake values, the RE−SE difference was higher in patients not receiving remifentanil only at setting of the first trochar.

The third finding was that intubation was associated with greater increases in RE, SE, and RE−SE difference than commencement of surgery. None of the indices

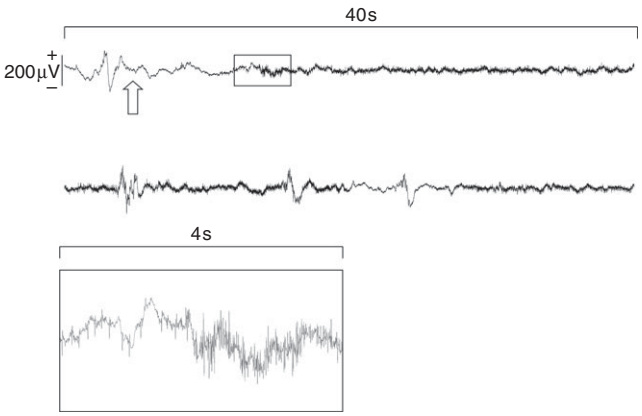

Fig 4 Two successive 40 s samples of EEG which show development of EMG after intubation (arrow upward) during EEG burst suppression. The box below is an enlarged 4 s piece of the signal, showing the beginning of EMG activity.

showed increased values at skin incision. This is in line with earlier literature, ranking endotracheal intubation as a stronger nociceptive stimulus than skin incision.[12]

The fourth and perhaps the most significant finding was that increased index values during nociceptive stimuli were strongly associated with the presence of EMG, confirmed by visual analysis of the raw biosignal and by the analysis of the spectrogram; both performed without knowledge of anaesthesia regimen. Spectral analysis of the biosignal demonstrated an EMG-associated change in the spectrum at $<20-100$ Hz.

After endotracheal intubation, no continuous EMG activity in the raw signal, or significant RE−SE difference in Entropy values, was noted in patients receiving remifentanil. EMG was more frequently present during surgical manipulation in patients without remifentanil. The reactivity of upper facial biosignal was seen in nearly all patients during intubation, in spite of lower RE and SE values than was the case during commencement of surgery. This could be explained by the high stimulus intensity of laryngoscopy and intubation[13 14] that elicits EMG activity also in patients receiving remifentanil. Another postulation might be the modelling of remifentanil pharmacokinetics: as the estimated effect-site remifentanil concentration is based on the cortical electrical activity,[10] it is theoretically possible that the drug concentration was lower than assumed in the areas controlling EMG. The EMG recorded is likely to be both from facial- and trigeminal-innervated muscles as the electrodes are on frontal and temporal muscles. The pathways to frontal and temporal muscles are the facial and trigeminal nerves, respectively, both originating from the brain stem.[15] The K_{e0} for remifentanil effect at the brain stem might differ from that measured as a change in EEG. The mean duration of 30 min from anaesthetic induction to skin incision, on the other hand, was sufficient to complete the saturation of remifentanil, abolishing the reactivity of EMG. Finally, as one of the electrodes in the Entropy strip is placed on the patient's temple, it is possible that the EMG activity during laryngoscopy and intubation comes partly from the temporal muscle, instead of the frontal muscle. Further research is needed to elucidate the behaviour of EMG during intubation.

In analysis of Entropy and raw EEG signal, the presence of EMG dictated Entropy values during nociceptive events. Typically, RE values increased with short delay, as described earlier by Vakkuri and colleagues.[6] In the majority of cases, the increase of RE was soon followed by an increase in SE values, decreasing the RE−SE difference. The increase in SE values was most probably due to the increase in biosignal activity below 32 Hz, as depicted in Figure 2. While all activity below 32 Hz is regarded as EEG in the analysis of Entropy,[5] strong EMG impact starts to change the spectrum already at 20 Hz.[16] This may explain the unexpected behaviour of SE during nociceptive stimuli, when anaesthesia regimen does not include adequate anti-nociception or effective neuromuscular block. Nociception-associated EMG activity may increase SE values, because the content of the biosignal starts to change already below 20 Hz (Fig. 2).

HR is a standard indicator of nociception. In this study, HR differed between the groups from intubation to the end of the study. Higher values were seen in patients without remifentanil. This may indicate stronger nociceptive input in these patients, although the direct effect of remifentanil on HR should also be considered.[17] The poor correlation between HR and RE−SE difference was most probably due to the widespread nociception-elicited alterations in EEG, reducing the RE−SE difference, as described above.

On the basis of our results, it is appropriate to conclude that Entropy RE−SE difference may increase during strong nociceptive stimuli, but this increase is often transient, due to increasing SE values. Therefore, although high SE values serve as an indicator of impending awareness, EMG contamination can associate with high SE values during otherwise sufficient hypnotic state of anaesthesia. Adequate anti-nociceptive medication, however, decreases the risk of EMG contamination, as seen in our patients receiving remifentanil.

One might argue that increasing SE levels in our study indicate less adequate anaesthetic depth and impending arousal. From a theoretical point of view, that is well possible. However, the connection between EMG, spectral characteristics of EEG, and SE was well demonstrated in the present study. EMG is generated at brain stem level; therefore, the presence of EMG is not a direct indicator of awareness. Moreover, appearance of EMG does not necessarily alter the underlying EEG signal during anaesthesia. As an example, in Figure 4, the burst suppression EEG signal remained unaltered, although strong EMG activity contaminated the signal. Finally, none of our patients had recall despite high SE values, although the study remains underpowered to examine awareness.

The biosignal was visually analysed by a single neurophysiologist with considerable experience on anaesthesia-

related EEG. No artifacts that could contribute significantly to the frequency bands above 32 Hz were detected in this analysis. As shown in Figure 3, electrical noise appears as a narrow band at 50 Hz, whereas electro-oculogram and ECG artifacts are limited at low frequency areas, instead of widespread EMG activity. With the aid of spectral presentation, EMG is reliably detected in EEG.

The intraoperative EMG contamination of EEG is challenging for an anaesthetist, because such low-amplitude activity is not always readily seen on monitor, even though the displaying of 'raw' EEG signal is highly recommended. The EMG-associated increase in SE value does not directly possess the risk of unintentional awareness during anaesthesia, because high SE value usually leads to re-adjustment of hypnotics. When remaining undetected, the situation could, however, cause inappropriate and potentially harmful use of anaesthetics.

The anaesthetic regimen of this study does not reflect our routine clinical practice and necessitates a comment. Our aim was to study the magnitude of RE−SE difference with or without strong anti-nociceptive medication, and without confounding impact of NMBAs. Nitrous oxide, however, was used as a baseline anti-nociceptive agent in our intubated patients under controlled ventilation. In most cases, endotracheal intubation and commencement of surgery went smoothly, whereas difficulties in intubation were faced in two patients, who were discarded from the study. Owing to the gentle manipulating techniques and used rescue medication, none of the patients reported any anaesthesia-related sequelae. With this technique, we were able to demonstrate the effects of EMG on the Entropy indices RE and, especially, SE. As neuromuscular blockers were not used, the impact of them remains to be studied later on.

In conclusion, we showed that Entropy RE−SE difference cannot reliably be used as an indicator of nociception in patients anaesthetized with propofol, nitrous oxide, and remifentanil without NMBAs. EMG activity can contaminate the interpretation, especially by increasing SE values. Further research is needed to elucidate the effects of EMG in detail, and to study the effect of neuromuscular blocking agents on EMG signal.

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NEUROSCIENCES AND NEUROANAESTHESIA

Explaining Entropy responses after a noxious stimulus, with or without neuromuscular blocking agents, by means of the raw electroencephalographic and electromyographic characteristics

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Key points

- Skin incision may cause simultaneous EMG and EEG arousals, sometimes only EEG arousal is detected.
- The respective power spectra of EEG and EMG overlap significantly at frequencies of 20–50 Hz.
- Response Entropy is susceptible to the use of rocuronium, limiting its usefulness in detecting nociception.
- In cases of misleading numerical values, the correct interpretation of the raw signal is necessary.

Background. Entropy™, an anaesthetic EEG monitoring method, yields two parameters: State Entropy (SE) and Response Entropy (RE). SE reflects the hypnotic level of the patient. RE covers also the EMG-dominant part of the frequency spectrum, reflecting the upper facial EMG response to noxious stimulation. We studied the EEG, EMG, and Entropy values before and after skin incision, and the effect of rocuronium on Entropy and EMG at skin incision during sevoflurane–nitrous oxide (N_2O) anaesthesia.

Methods. Thirty-eight patients were anaesthetized with sevoflurane–N_2O or sevoflurane–N_2O–rocuronium. The biosignal was stored and analysed off-line to detect EEG patterns, EMG, and artifacts. The signal, its power spectrum, SE, RE, and RE–SE values were analysed before and after skin incision. The EEG arousal was classified as β (increase in over 8 Hz activity and decrease in under 4 Hz activity with a typical β pattern) or δ (increase in under 4 Hz activity with the characteristic rhythmic δ pattern and a decrease in over 8 Hz activity).

Results. The EEG arousal appeared in 17 of 19 and 15 of 19 patients (NS), and the EMG arousal in 0 of 19 and 13 of 19 patients ($P<0.01$) with and without rocuronium, respectively. Both β ($n=30$) and EMG arousals increased SE and RE. The δ arousal ($n=2$) decreased both SE and RE. A significant increase in RE–SE values was only seen in patients without rocuronium.

Conclusions. During sevoflurane–N_2O anaesthesia, both EEG and EMG arousals were seen. β and δ arousals had opposite effects on the Entropy values. The EMG arousal was abolished by rocuronium at the train of four level 0/4.

Keywords: anaesthetics volatile, sevoflurane; depth of anaesthesia; measurement techniques, electromyography; monitoring, electroencephalography; neuromuscular block, rocuronium

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One of the commercially available depth of anaesthesia monitors based on EEG is M-Entropy™ module (GE Healthcare, Helsinki, Finland), which calculates the characteristics of upper facial biosignal with an analysis of time–frequency balanced spectral entropy, taking into account the amount of suppressed EEG signal. The resulting index of EEG and EMG activities, Entropy, has been shown to be a valid indicator of the hypnotic effect of propofol, thiopental, isoflurane, sevoflurane, and desflurane.[1]

Entropy yields two parameters: State Entropy (SE) and Response Entropy (RE). SE, computed over the EEG-dominant (0.8–32 Hz) frequency range, reflects the cortical state of the patient. RE, computed over the EEG- and EMG-dominant frequency ranges (0.8–47 Hz), serves at least partly as an indicator of upper facial EMG activation,[2] which has been shown to represent nociception or impending awakening.[3]

The studies about the effect of neuromuscular blocking agents (NMBAs) on the depth of anaesthesia monitors have been conducted under many different study regimens and in different surgical settings, so they have yielded different results. First, EMG has been reported to influence the reliability of the depth of anaesthesia monitors.[4] The

Bispectral Index™ (BIS) values have been falsely elevated by EMG activity in anaesthetized and sedated patients.[5 6] However, during deep propofol anaesthesia (BIS<50) without nociceptive stimuli, NMBAs did not have an effect on the BIS values.[7 8] Low-frequency (<32 Hz) EMG activity has led to misleading Entropy values during propofol anaesthesia without NMBAs.[9] It has been reported that rocuronium alters the RE and RE–SE responses to laryngoscopy[10] and that the rocuronium-induced alteration in the RE–SE response to intubation is dose-dependent.[11]

Since the introduction of Entropy in 2004, its behaviour during anaesthesia and nociceptive stimuli has been studied extensively. In these studies, the focus has been on the numerical values, and the analysis of the signal *per se* has been neglected. The original biosignal, or even the spectral analysis of the biosignal, has only rarely been compared with the index values.[9]

The primary endpoint of this study was the behaviour of original biosignal, both its visual appearance and spectral content for EEG and EMG signs of arousal, before and after skin incision during sevoflurane–nitrous oxide (N_2O) anaesthesia, in patients with or without rocuronium. The secondary endpoints were the effects of EMG and EEG arousals on the Entropy parameters, and the effect of rocuronium on the Entropy's numerical values.

Methods

This study followed the design of a prospective clinical study. After the approval of the local Ethics Committee and Finnish National Agency for Medicines and after written informed consent, 39 female patients undergoing laparoscopic gynaecological surgery were studied. Inclusion criteria were: expected duration of operation >30 min, age 18–60 yr, and ASA physical status I or II. Patients were excluded if they had a disease or an injury affecting the central nervous system, alcohol or drug abuse, or BMI >28. All patients fasted overnight before surgery.

Anaesthesia and study protocol

The original biosignal, Entropy parameters calculated from the biosignal, and vital signs were collected on a laptop computer under two anaesthetic regimens, both of which included premedication with diazepam 10 mg p.o. Premedication was given to all patients 60 min before induction of anaesthesia. An i.v. route was established for all patients and an infusion of isotonic saline was started. Intermittent non-invasive arterial pressure was recorded every 5 min. Electrocardiogram, inspired fractions (F_I), end-tidal concentrations of anaesthetic gases and CO_2, and peripheral oxygen saturation were continuously monitored with the Datex-Ohmeda S/5™ Anaesthesia Monitor.

Twenty patients were administered propofol 1 mg kg^{-1} i.v., followed by manually controlled ventilation with 8% sevoflurane in a 67% N_2O–oxygen mixture via a face mask. Tracheal intubation was performed, as gently as possible, 150 s later. If intubation difficulties were met, mask ventilation was restarted and another intubation attempt was made 1–3 min later. If the second attempt was unsuccessful, rocuronium was given and the patient was discarded from the study. After securing the airway, controlled mechanical ventilation was started with a fresh flow of 6 litre min^{-1} (67% N_2O in oxygen). To facilitate the intubation conditions, relatively high sevoflurane concentrations (up to 8%) were used before laryngoscopy. After successful intubation, the sevoflurane concentration was adjusted to keep SE between 40 and 60, the target value being 50. In the case of an increase in SE above 65, as a rescue medication, the sevoflurane vaporizer was adjusted according to the anaesthesiologist's judgement, up to maximum (F_I 8%), in order to prevent awareness. After a rescue bolus of sevoflurane, the sevoflurane vaporizer was readjusted once the SE values decreased below 60.

Nineteen patients were anaesthetized the same way as described above, but once the entropy values decreased below 50, patients received rocuronium 0.6 mg kg^{-1}. Tracheal intubation was performed after neuromuscular transmission was 0/4. Neuromuscular transmission was monitored with the M-NMT Mechanosensor™ (Datex-Ohmeda, Helsinki, Finland) and assessed using the train of four (TOF) stimulation mode. The calibration of the Mechanosensor was performed in all patients according to the manufacturer's guidelines before NMBA administration.

After tracheal intubation, commencement of ventilation, and preparing the patient for surgery, the permission to start laparoscopy was granted. Before surgical manipulation, the patient was not touched or otherwise disturbed for 5 min to ensure artifact-free data collection. The setting of the patient to the gynaecological position, washing of the abdomen, application of the sterile drapes, and the 5 min equilibrium period amounted to a mean of 21 and 29 min between intubation and skin incision in groups with and without NMBAs, respectively. An additional 10 mg bolus of rocuronium was given for eight patients, whose TOF exceeded 0/4. The study was completed 1 min after setting of the first laparoscopy trochar. Thereafter, the administration of N_2O was discontinued and the patient's lungs were ventilated with air/O_2 ($F_{I_{O_2}}$ 0.33). After completion of the study period, fentanyl and rocuronium were given according to clinical needs. All patients were interviewed during the first postoperative day, regarding their possible anaesthesia- and surgery-related memories and intubation-associated sequelae. Furthermore, the patients were encouraged to report their possible operation-related memories later on to the researchers by phone.

EEG acquisition

Entropy monitoring started before induction of anaesthesia and continued uninterrupted until the end of the study. The forehead biosignal was collected with a disposable electrode strip (Entropy Sensor, GE Healthcare) for Entropy measurement. After de-greasing of the forehead skin using 70% isopropanol, the strip was positioned as recommended

by the manufacturer. The signal was acquired from two electrodes of the strip: one frontally in the midline, 2 cm above the eyebrows, and the other 2 cm laterally from the outer canthus of the left eye. The first electrode was on the frontal muscle, recording the EEG from the frontal poles, and the second electrode was on the orbicularis oculi and temporal muscles, recording the EEG from the frontal and temporal lobes, including the basal forebrain and the mesial temporal cortex. The EEG was collected with an Entropy Module of the S/5™ Anaesthesia Monitor (GE Healthcare), with a sampling rate of 400 Hz. High- and low-pass filters of 0.5 and 118 Hz (−3 dB; 60 dB/decade), respectively, were applied. A power-line artifact at 50 Hz was not filtered. The EEG was downloaded and stored on a laptop computer with S5 Collect software (GE Healthcare).

Analyses of the biosignal

The raw signal was analysed with high resolution, and with the power spectrum. The typical EMG pattern in the original signal, with a considerable power increase of above 40 Hz, was classified as EMG arousal. The depression of δ (<4 Hz) activity, increase in over 8 Hz activity, and minimal increase of above 40 Hz, together with the characteristic β pattern, were classified as β arousal. Skin incision-associated increase in δ activity and a simultaneous decrease in over 8 Hz activity were classified as δ arousal.

Spectrogram, that is, a presentation of the spectral content of a biosignal, was produced with Somnologica™ sleep analysis program (Medcare Flaga, Reykjavik, Iceland). In such a presentation, power spectra of consecutive 1.0 s samples of the signal are calculated and presented vertically in the direction of the *y*-axis and plotted against time in the *x*-axis. The density (i.e. 'darkness') of the spectrogram reveals the amount of activity at the respective frequency. Thus, the spectrogram presents the same information as successive power spectra, but in a compressed form. A power-line artifact is seen in the spectrogram as a sharp activity band at 50 Hz, and an ECG or electro-oculogram artifact is typically located at a rather low-frequency range. Therefore, an EMG is virtually the only artifact that is displayed over a wide frequency range.

In statistical analyses, RE and SE values were analysed off-line as a mean of 15 s (three consecutive readings collected by the S5 Collect software) 1 min before and 1 min after commencement of surgery. The RE–SE difference was calculated by subtracting the SE value from the simultaneous RE value.

Both the raw biosignal and the spectrogram at the time point of skin incision were inspected visually off-line, without knowledge of the behaviour of Entropy indices, by an experienced clinical neurophysiologist (V.J.), to judge the presence or absence of an EMG. Later on, all authors, to ensure the agreement of the detections, analysed the traces and classifications jointly. To analyse the effect of EMG on the EEG spectrum, power spectra before and after commencement of surgery were drawn in all patients. In the calculation of the power spectrum, a window of 10 s was used.

Statistical methods

Owing to the fact that the actual biosignal has not been previously studied in the present setting, the power calculation was based on the behaviour of RE–SE difference, a phenomenon thought to reflect EMG activation. In the power calculation, the results of Hans and colleagues[10] (RE–SE difference of 4 units with rocuronium and 11 units without rocuronium, SD 6 units) were utilized. Because sevoflurane and N_2O possess anti-nociceptive properties (in the study by Hans and colleagues, propofol was used as an anaesthetic agent), a 50% reduction in the RE–SE difference and the SD was assumed. To test whether the RE–SE difference is lower when NMBAs are used, the study was designed to have a power of 80% to detect a statistical significance in the RE–SE difference between groups with and without rocuronium, assuming a two-sided α level of 0.05, with nociception-associated mean RE–SE differences of 2 and 5.5 units (SD 3 units) between groups, respectively. To meet the criteria of power calculation, 12.5 patients per group would be needed. All statistical analyses were performed using SPSS for Windows software (version 16.0, SPSS, Chicago, IL, USA). One-way analysis of variance (ANOVA), followed by *t*-tests were performed for parametric data, or by χ^2 tests for non-parametric comparisons, where appropriate. A value $P<0.05$ was considered statistically significant.

Results

One enrolled patient without rocuronium was excluded because of problems in laryngoscopy and intubation. All others were successfully intubated with one or two attempts. Therefore, 19 patients receiving sevoflurane–N_2O and 19 patients receiving sevoflurane–N_2O–rocuronium were studied. Patient characteristics did not differ between groups. The mean ages of patients in the sevoflurane–N_2O group and those in the sevoflurane–N_2O–rocuronium group were 33 and 31 yr, mean weights were 66 and 63 kg, and mean heights were 167 and 167 cm, respectively.

Before skin incision, rescue medication, that is, a rapid increase in inspired sevoflurane concentration, was given to five patients (three with and two without rocuronium). These boluses were given 5, 5, 6, 12, and 13 min before skin incision, respectively.

Skin incision caused a decrease in EEG δ activity and an increase in over 8 Hz activity in 15 patients with rocuronium and in 15 patients without rocuronium. Simultaneous EMG occurred in 13 of the subjects not receiving rocuronium. No EMG was seen in patients with rocuronium ($P<0.001$). After skin incision, rescue medication was given to 24 patients (9 and 15 patients with and without rocuronium, respectively). The rescue medication was followed by a decrease in over 8 Hz activity and by an increase in δ activity. However, EMG activity continued. In this study, the EMG never appeared without the β arousal. In two patients not receiving rocuronium, the β arousal appeared without the EMG. The incidence of detected EMG in both groups, and the association

between the EMG and the RE–SE difference, RE, and SE, is given in Table 1.

The spectrogram, RE and SE values, end-tidal sevoflurane concentration, and heart rate from the awake state until the end of the study period in an example patient are depicted in Figure 1.

In two patients with rocuronium, the EEG arousal was classified as δ arousal. The δ arousal consisted of an increase in high-amplitude δ activity and a decrease in over 8 Hz activity. Figure 2 shows an example of a δ arousal and its effects on Entropy's numerical values, 8–13 and 0.5–4 Hz frequency bands, the original biosignal, and the power spectra before and after the arousal.

Rocuronium altered the entropy RE–SE response to skin incision. The skin incision produced a significant increase in RE and SE in both groups, whereas RE–SE increased only in patients without rocuronium. After skin incision, there were significant between-group differences in RE and RE–SE (Fig. 3). Heart rate before skin incision was higher in patients with rocuronium than in those without rocuronium. Skin incision caused an increase in heart rate in both groups.

Discussion

The first finding in our study was that skin incision caused both EMG and EEG arousals. The two arousals often occurred simultaneously, but in some patients, only the EEG arousal was detected. In patients receiving rocuronium, the EMG arousal was abolished and only the EEG arousal was seen. Most EEG arousals consisted of mixed high-amplitude slow activity turning into higher frequency low-amplitude activity, that is, β arousal. In two patients, skin incision caused a mixed frequency EEG to turn into high-amplitude δ activity and the vanishing of the high-frequency activity, that is, δ arousal. The δ arousal is also called 'paradoxical' or 'reverse' arousal.[12]

Spectral entropy yields high values when the power spectrum is flat and low values when the power spectrum is more uneven.[2] During deepening anaesthesia, the slow activity in the EEG gradually increases, producing an increasing spectral peak at the lower frequency edge of the power spectrum, and this causes a decrease in spectral entropy, and correspondingly, a decrease in RE and SE.

The EMG and β arousals cause an increase in Entropy values and lead the anaesthesiologist to deepen the level of anaesthesia. The EMG contamination of EEG can lead to overdosing of anaesthetic agents. The δ arousal and the following decrease in SE values, if interpreted incorrectly, can lead to decreasing of the anaesthetic concentration, therefore increasing the risk of intraoperative awareness. It has been suggested that the δ arousal occurs when a patient is exposed to surgical stimuli during inadequate analgesia.[13 14] The neurophysiological mechanisms of arousal during anaesthesia are poorly known. They are probably closely related to arousal mechanisms of sleep, which can also produce both β and δ arousals, especially in children.[15] Studies done with cats indicate that slow EEG δ activity may

Table 1 Incidence of detected EMG in both groups, and the association between EMG and RE–SE difference, RE, and SE

Time point	EMG present/absent			RE–SE			RE			SE		
	Sevoflurane–N_2O	Sevoflurane–N_2O–rocuronium	*P*-value (Fisher's exact test)	EMG present	EMG absent	*P*-value (*t*-test)	EMG present	EMG absent	*P*-value (*t*-test)	EMG present	EMG absent	*P*-value (*t*-test)
Before surgery	2/17	0/19	0.486	9 (1.4)	0.64 (0.68)	0.07	50 (11)	41 (9)	0.446	40 (10)	40 (8)	0.992
After surgery	13/6	0/19	<0.001	11.2 (3.1)	1.08 (1.29)	<0.001	77 (17)	48 (16)	<0.001	66 (15)	46 (16)	0.001

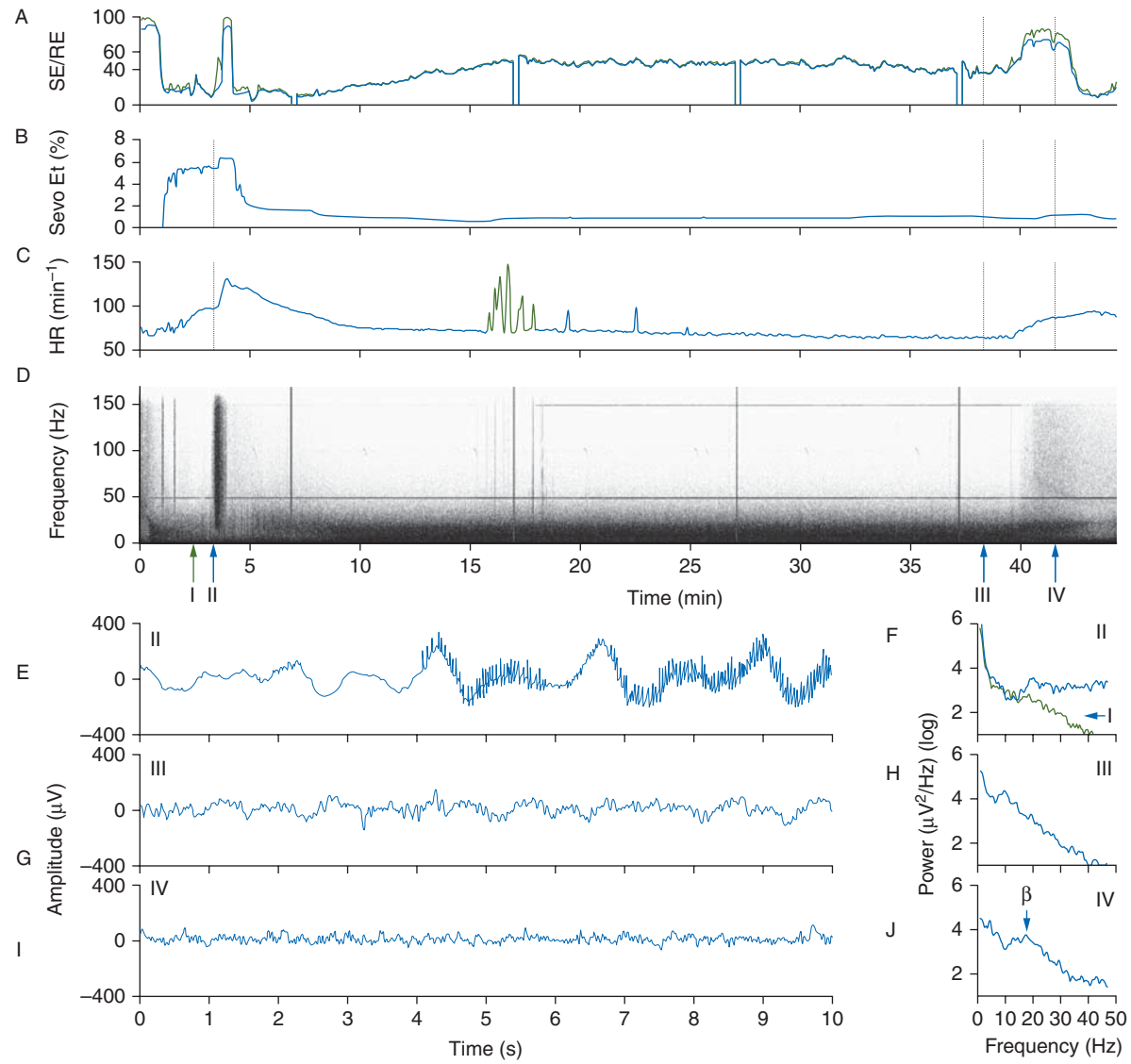

Fig 1 The whole study period in one patient anaesthetized without rocuronium. (A) The numerical values of SE and RE. (B) The end-tidal sevoflurane concentration. (C) Heart rate. The artifacts at ~16 min caused by patient positioning have been dimmed. (D) The spectrogram of the signal recorded with Entropy sensor. The Roman numeral 'I' refers to the time point of the power spectrum before intubation, shown as dimmed line in (F). The Roman numerals II, III, and IV refer to the 10 s samples of the original biosignal and to the corresponding power spectra, presented in (E–J). (E) A 10 s sample of the original biosignal at the time of intubation. EMG causes an increase in SE and RE values to maximum. The EEG, however, shows high voltage slow activity which together with high end-tidal sevoflurane concentration, suggests that the patient was deeply unconscious. (F) The respective power spectrum from the same time period. EMG causes a typical increase in the high frequencies of the spectrum. (G) A 10 s sample of the original biosignal ~1 min before skin incision, showing mixed activity. (H) The respective power spectrum from the same period, showing δ activity and a peak around 10 Hz (α activity). (I) A 10 s sample of the original biosignal shortly after the beginning of the operation, showing β activity. (J) The respective power spectrum of (I). A decrease in low frequencies and increased β activity at ~20 Hz indicate EEG arousal. The β activity causes the power spectrum to be more even and flat, increasing the SE and RE to almost awake values, although the patient is in surgical anaesthesia. The raw signal is distinctly different from a typical awake signal. The power at 30–50 Hz also increases during β arousal, which is visible in the spectrogram.

be related to the activation of the reticular formation of the brainstem.[16]

An example of the δ arousal after skin incision, that is, an increase in δ activity and a decrease in over 8 Hz activity, is shown in Figure 2. In the logarithmic power spectrum, the peak on the left increases, while activity around 20 Hz decreases. This produces a more peaked and uneven power spectrum with a corresponding decrease in spectral entropy. The RE and SE values decrease to levels of deep anaesthesia, usually seen during almost continuous EEG suppression. In the recording displayed in Figure 2, however, no EEG suppressions appeared.

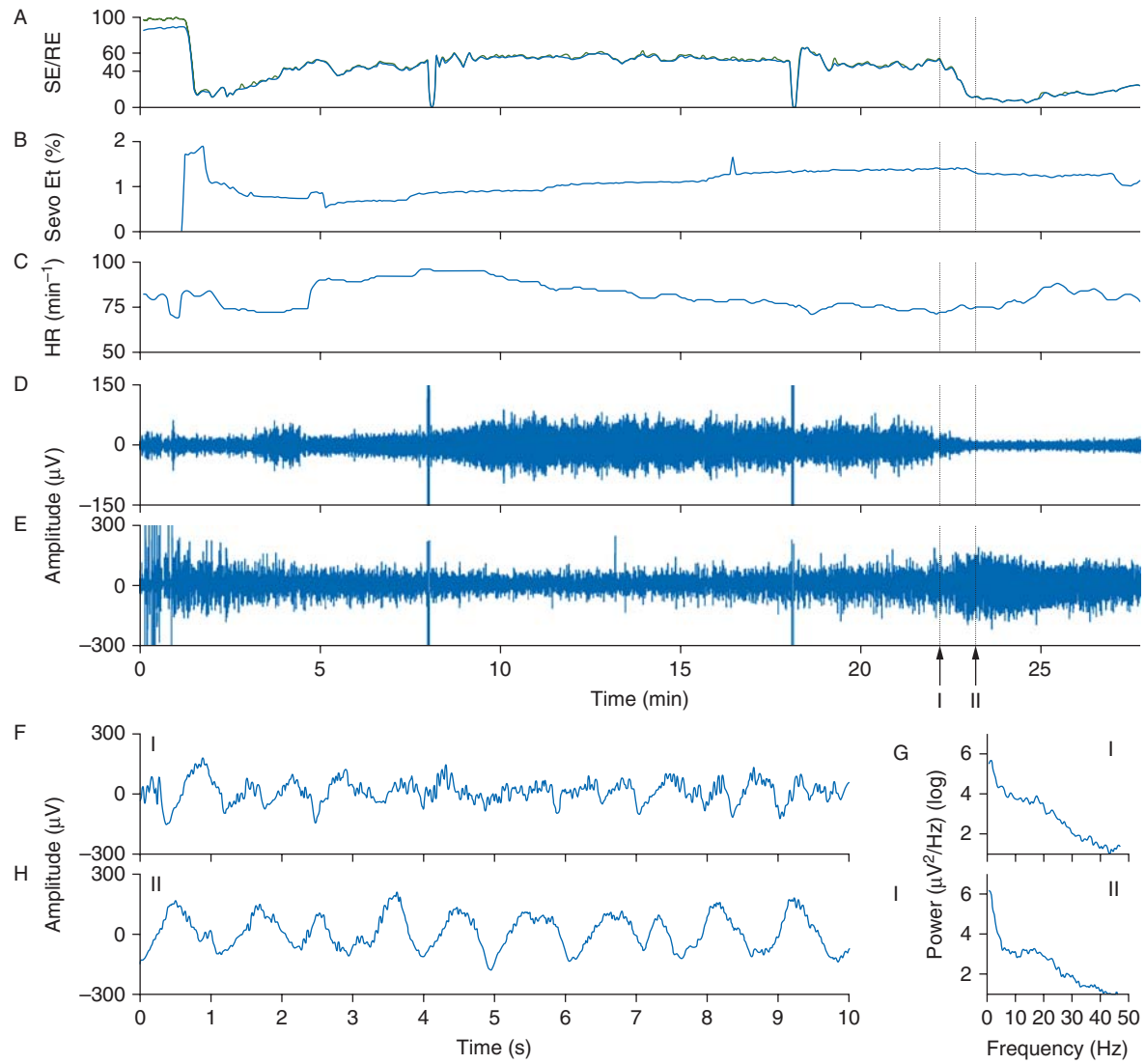

Fig 2 The whole study period in one patient anaesthetized with sevoflurane–N_2O–rocuronium. (A) The numerical values of SE and RE. (B) The end-tidal sevoflurane concentration. (C) Heart rate. (D) Band-pass-filtered EEG 8–13 Hz (α activity); plotted strongly compressed to demonstrate amplitude changes. (E) Band-pass-filtered EEG 0.5–4 Hz, i.e. δ activity. (F and G) A 10 s sample of the original biosignal and the respective power spectrum; plotted from a time point I (before skin incision). (H and I) A 10 s sample of the original biosignal and power spectrum from the time point II (after skin incision).

Our second observation was the considerable EMG activity already at frequencies <20 Hz and EEG β activity exceeding 20 Hz, demonstrating that the respective power spectra of EEG and EMG overlap significantly (Fig. 1). Owing to their overlapping power spectra, the contribution of the EEG and the EMG cannot be accurately separated by Entropy. Visually, it is sometimes impossible to distinguish between β activity and the EMG in sleep or anaesthesia recordings, as the EMG generated at a distance from the recording electrodes loses its sharp, spiky appearance. In our opinion, this finding explains the numerous reports where NMBAs have been shown to have an effect on numerical values of the depth of anaesthesia monitors.[6 17] It also helps us understand why the effect of NMBAs on the depth of anaesthesia monitors varies from one setting to another. The level of anaesthesia, the presence or absence of nociceptive stimuli, the use of anti-nociceptive medication, patient anxiety, and possibly many other confounding factors have contributed to different findings in previous studies.[4–8 10 11] Therefore, in future studies, one should focus both on the original biosignal in the time and frequency domain and on the numerical values of the depth of anaesthesia monitors.

Finally, the third finding in our study was the change in the numerical values of RE, SE, and RE–SE during skin incision. In patients without rocuronium, skin incision caused a significant increase in RE, SE, and RE–SE. In patients receiving rocuronium, skin incision caused a significant increase in RE and SE, whereas no change was detected in RE–SE. After

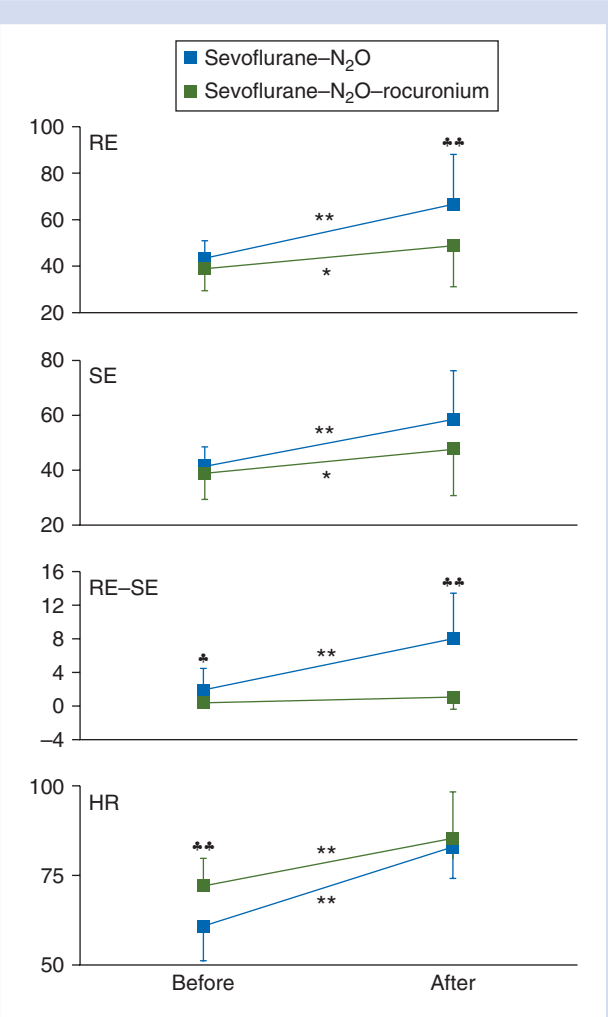

Fig 3 The behaviour of RE, SE, RE–SE, and HR (mean+SD) 1 min before and 1 min after skin incision in patients anaesthetized with sevoflurane–N_2O or sevoflurane–N_2O–rocuronium. ♣$P<0.05$ and ♣♣$P<0.01$ between the groups; *$P<0.05$ and **$P<0.01$ within the groups.

skin incision, RE and RE–SE were lower in patients with rocuronium. The behaviour of RE, SE, and RE–SE during commencement of surgery leads us to suggest that Entropy monitoring is susceptible to the use of rocuronium, limiting the usefulness of RE and RE–SE in detecting nociception with a strong neuromuscular block.

A direct effect of NMBAs on the depth of anaesthesia has also been suggested. A controversial 'afferent muscle spindle' theory postulates that NMBAs would reduce the muscle tone and the amount of proprioceptive inputs to the reticulo-thalamic activating system, thus reducing the level of arousal,[18] an assumption supported by some studies,[19 20] but also disputed by some more recent studies.[21 17] Before skin incision, end-tidal sevoflurane concentrations in groups with and without rocuronium were 1.11 (0.23) and 1.01 (0.32), respectively (NS). However, since our study design and power analysis were not intended to address the afferent muscle spindle theory, we cannot comment on it.

The behaviour of heart rate during commencement of surgery was not very surprising, as heart rate is often regarded as a standard indicator of nociception. As to why the heart rate before commencement of surgery was higher in patients receiving rocuronium, we have two possible explanations. First, rocuronium may release histamine, thus raising heart rate, although the histamine-releasing effect has been described only after rocuronium doses of >1.2 mg kg^{-1}.[22] Secondly, rocuronium is a potentially vagolytic drug, therefore increasing heart rate. Both of these explanations are not totally satisfying and the true nature of the increased heart rate in patients receiving rocuronium may remain unrevealed. Interestingly, also Hans and colleagues[10] reported a higher heart rate in patients receiving rocuronium, but they concluded that a higher heart rate was not clinically significant and that the difference in heart rate did not change during intubation.

The characteristic patterns of signal and its power spectrum allowed us to classify β and EMG arousals. However, they often occur simultaneously, and to more accurately detect them, more than one channel should be recorded. In this study, we were restricted to the single-channel recording of the Entropy monitor.

In conclusion, skin incision can cause both EEG and EMG arousals. EEG arousal can be either β or δ arousal. The β and EMG arousals increase the Entropy values, leading the anaesthesiologist to increase the concentration of anaesthetic agents. The δ arousal decreases the Entropy values and may lead the anaesthesiologist to falsely decrease the concentration of the anaesthetic agent. To avoid misinterpretation of the depth of anaesthesia indices, the display and correct interpretation of the raw signal is necessary.[23] All anaesthesiologists using these monitors should be familiar with the effects of EMG and EEG arousal patterns and understand why they may cause misleading index values.

Conflict of interest

A.Y.-H. is a paid consultant for GE Healthcare Finland.

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Elevated BIS and Entropy values after sugammadex or neostigmine: an electroencephalographic or electromyographic phenomenon?

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Background: Sugammadex is designed to antagonize neuromuscular blockade (NMB) induced by rocuronium or vecuronium. In clinical practice, we have noticed a rise in the numerical values of bispectral index (BIS) and Entropy, two electroencephalogram (EEG) – based depth of anesthesia monitors, during the reversal of the NMB with sugammadex. The aim of this prospective, randomized, double-blind study was to test this impression and to compare the effects of sugammadex and neostigmine on the BIS and Entropy values during the reversal of the NMB.
Methods: Thirty patients undergoing gynecological operations were studied. Patients were anesthetized with target-controlled infusions of propofol and remifentanil, and rocuronium was used to induce NMB. After operation, during light propofol-remifentanil anesthesia, NMB was antagonized with sugammadex or neostigmine. During the following 5 min, the numerical values of BIS, BIS electromyographic (BIS EMG) and Entropy were recorded on a laptop computer, as well as the biosignal recorded by the Entropy strip. The Entropy biosignal was studied off-line both in time and frequency domain to see if NMB reversal causes changes in EEG.
Results: In some patients, administration of sugammadex or neostigmine caused a significant rise in the numerical values of BIS, BIS EMG and Entropy. This phenomenon was most likely caused by increased electromyographic (EMG) activity. The administration of sugammadex or neostigmine appeared to have only minimal effect on EEG.
Conclusion: The EMG contamination of EEG causes BIS and Entropy values to rise during reversal of rocuronium-induced NMB in light propofol-remifentanil anesthesia.

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Monitoring patients during general anesthesia with electroencephalogram (EEG) – based depth of anesthesia (DoA) monitors has become routine in clinical practice. The most established DoA monitor is the bispectral index (BIS™, Aspect Medical Systems, Newton, MA, USA).[1] The information produced by BIS on the anesthesia monitor includes: BIS index scaled from 100 (awake) to 0 (suppressed EEG signal), signal quality index, electromyographic (BIS EMG) activity and suppression ratio. Another commercially available DoA monitor is Entropy (M-Entropy™ module, GE Healthcare, Helsinki, Finland).[2] Entropy yields two parameters, State Entropy (SE) and Response Entropy (RE). SE is calculated from the 0.8–32 Hz frequency range and ranges from 0 to 91. RE is calculated from the 0.8–47 Hz frequency range. RE is equal to or higher than SE and ranges from 0 to 100. The difference between RE and SE (RE-SE) is thought to reflect EMG activity, a sign of impending arousal or inadequate anesthesia.[3]

The reliability of BIS and Entropy monitors has been shown to be influenced by EMG activity.[4,5,6] Sugammadex (Bridion®, N. V. Organon, Oss, the Netherlands) is a recently introduced cyclodextrin-derived drug designed to reverse neuromuscular blockade (NMB) induced by rocuronium or vecuronium.[7] Sugammadex is a rapidly acting drug reversing even deep NMB in 3 min.[8] In one study, the administration of sugammadex during propofol-fentanyl anesthesia has been associated with an increase in BIS values.[9] However, during deep (BIS 30–33) propofol-remifentanil anesthesia, reversal of NMB by sugammadex did not increase BIS or

Entropy values.[10] Neostigmine, an anticholinesterase agent commonly used to antagonize NMB, has also been shown to elevate BIS values during reversal of NMB in patients anesthetized with propofol and remifentanil.[11] The relationship between neuromuscular blocking agents and DoA, and, on the other hand, between reversal of NMB and DoA have been studied widely.[9,11–13] The results of these studies have been contradictory. It has been suggested that NMB reduces proprioceptive input emerging from the peripheral receptors to the brain, thus influencing DoA or at least DoA monitors. This so-called de-afferentation theory has got support from some studies, but it has also been disputed by other studies.[14,15,16]

We have noticed clinically that reversal of NMB with sugammadex may produce a rise in the numerical values of BIS and Entropy, while neostigmine seems to rise the index values less and/or more seldom and/or more gradually. Our clinical impression and the different results obtained from previous studies inspired us to compare the effects of sugammadex and neostigmine on BIS, BIS EMG, SE, RE and EMG arousal. This study was designed to test our hypothesis that sugammadex produces a greater and more frequent rise in DoA indexes than neostigmine.

The primary end point in our study was the change in the numerical values of Entropy and BIS in patients receiving sugammadex or neostigmine. The secondary end point was the changes detected in the Entropy biosignal when analyzed both in time and frequency domain. We hypothesized that sugammadex would increase the BIS and Entropy values more often than neostigmine and assumed that this increase in index values would be caused by EMG.

Methods

Patients

The study was approved by the Ethics Committee of Tampere University Hospital (R09041M) and by the Finnish National Agency for Medicines (KLnro 28/2009), and registered with EudraCT (2009-010916-14). The study was also registered with ClinicalTrials.gov under the US National Library of Medicine (Code NCT01142648).

After written informed consent, 30 female patients undergoing elective gynecological surgery were enrolled in this prospective, randomized, double-blind study. Patient enrolment started January 1, 2010 and ended March 31, 2010. Before any patients were enrolled in the study, sealed envelopes containing the assigned study drug were dropped into a cardboard box, and the envelopes were carefully mixed. On the day of the operation, an envelope was lifted from the box by the anesthesiologist in charge of the anesthesia (A.A.). The envelope was handed to an operating room nurse, who thereafter prepared the study drug in the absence of the anesthesiologist in charge. Inclusion criteria were an American Society of Anesthesiologists (ASA) score of I or II, body mass index < 30, and age 18–65 years. Exclusion criteria were disease or injury affecting central nervous system, alcohol or drug abuse, and allergy to any of the drugs used during anesthesia. All patients fasted overnight before surgery.

Anesthesia protocol

All patients were premedicated with diazepam 10 mg po, approximately 60 min before induction of anesthesia. An intravenous route was established and an infusion of isotonic saline was started. Standard monitoring with the Datex-Ohmeda S/5™ anesthesia monitor (GE Healthcare) included intermittent noninvasive blood pressure, a three-lead electrocardiogram, inspired fractions and end-tidal (Et) concentrations of oxygen, inspiratory and Et partial pressure of carbon dioxide and peripheral pulse oximetry. All patients were anesthetized with target-controlled infusions (TCI; Asena™ PK, Alaris Medical Systems, Basingstoke, UK) of propofol and remifentanil. Pharmacokinetic models of Schnider et al.[17] and Minto et al.[18] were utilized for administration of propofol and remifentanil, respectively. Effect-site concentrations (Ce) of propofol and remifentanil were adjusted according to the judgment of the anesthesiologist (A.A.) in charge. To facilitate endotracheal intubation, rocuronium 0.6 mg/kg was given. Thereafter, additional 5–10 mg doses of rocuronium were given if train of four (TOF) ratio exceeded 50%. After skin closure in the end of the operation, the patients were allocated to receive either sugammadex or neostigmine for the reversal of NMB. In the sugammadex group, the patients received 200 mg (= 2 ml) of sugammadex. In the neostigmine group, the patients received the standard NMB reversal agent in our institution, i.e. neostigmine 2.5 mg, and glycopyrrolate 0.5 mg to block the peripheral muscarinic side-effects of neostigmine (Glycostigmin®, Leiras, Turku, Finland). The original 1-ml mixture of neostigmine and glycopyrrolate was diluted to a volume of 2 ml with isotonic saline by an operating room nurse to ensure the similar appearance of the reversal agents, rendering the anesthesiologist blinded to the drug

used. To enhance the recovery, the estimated effect-site concentration of propofol was titrated to as close to 2.0 μg/ml as possible, but SE value was kept below 60 to avoid awareness. Also the estimated effect-site concentration of remifentanil was kept low (Ce 0.5–2.5). After the end of operation, surgical drapes were removed and the patient was positioned in supine position. Thereafter, the patient was not touched or otherwise disturbed, and the study drug was given only after the estimated effect-site concentrations of propofol and remifentanil had reached steady state. The administration of the study drug was followed by a 5-min study period, during which the numerical values of BIS, BIS EMG and Entropy were recorded on a laptop computer, as well as the biosignal recorded by the Entropy strip. The effect-site concentrations of propofol and remifentanil were kept unchanged until the end of the 5-min study period.

Neuromuscular monitoring

Neuromuscular function was assessed using M-NMT Mechanosensor™ using the TOF stimulation mode. After loss of consciousness, the calibration of the Mechanosensor was performed in all patients according to manufacturer's guidelines prior to rocuronium administration. The values measured by Mechanosensor were collected to a computer at 5-s intervals using S5 Collect software (GE Healthcare). Stimulation interval was 20 s from the administration of rocuronium to the intubation of the trachea. Endotracheal intubation was performed when TOF count was 0/4. After endotracheal intubation, the stimulation interval was changed to 1 min. After the end of surgery, the stimulation interval was changed to 20 s before reversal of the NMB.

BIS and Entropy monitoring

The monitoring of BIS and Entropy started before induction of anesthesia and continued uninterrupted until extubation of the trachea. For collection of BIS parameters, a disposable BIS Quatro™ sensor (Aspect Medical Systems) and E-BIS module for S/5™ anesthesia monitor (GE Healthcare) were used. The Entropy parameters and the forehead biosignal were collected with a disposable electrode strip (Entropy Sensor, GE Healthcare) for Entropy measurement. Following degreasing of the forehead skin using 70% isopropanol, the strips were positioned as recommended by the manufacturers. The sensors were randomly positioned so that the first sensor was placed lower on the forehead and on the left temple, and the second sensor was placed above the first sensor on the forehead, and then on the right temple. The temporal electrodes were positioned 2 cm laterally from the outer canthus of the eye. The frontal electrodes were on the frontal muscle, recording EEG from frontal pole, and the temporal electrodes were on the orbicularis oculi and temporal muscles, recording EEG from frontal and temporal lobes, including basal forebrain and mesial temporal cortex. All BIS and Entropy parameters were obtained from the monitor at 5-s intervals with S5 Collect software and saved on a laptop computer. The EEG was collected with an Entropy module of the S/5™ anesthesia monitor, with a sampling rate of 400 Hz. High- and low-pass filters of 0.5 and 118 Hz (–3 dB; 60 dB/decade), respectively, were applied. Power line artifact at 50 Hz was not filtered.

Analysis of the Entropy biosignal

The biosignal recorded by the Entropy strip during the 5-min study period was analyzed with high resolution in order to discover the electrophysiological phenomena that would explain the increasing index values. The analysis of the biosignal included: (1) visual inspection; (2) band-pass filtered EEG (0–4 Hz (delta), 4–8 Hz (theta), 8–13 Hz (alfa), 13–30 Hz (beta), 32–47 Hz (RE-SE) and 70–110 Hz (BIS EMG) frequency bands); (3) power spectra; and (4) spectrograms. The typical EMG pattern in the original biosignal, with a considerable power increase of above 40 Hz, led us to suggest that the change in BIS and Entropy values was caused by EMG. Owing to the overlapping power spectra of EEG and EMG, whenever a strong EMG activity is present, it is impossible to separate EEG from EMG. If we found no evidence of EMG in the biosignal after the administration of neostigmine or sugammadex, additional analysis of the biosignal was done. This additional analysis was done by calculating beta/delta ratio from successive 30-s samples of the biosignal and by calculating spectral edge frequency-95% (SEF95).

Classification of responses to NMB reversal

Because Entropy is the standard DoA monitoring method in our institution, we decided to classify the patient responses to the NMB reversal agents according to the change in SE values. The maximal rise in SE value above 80 was classified as a strong response; a maximal rise in SE value to 60–80 was classified as a weak response, and SE value remaining < 60 was classified as a nonresponse.

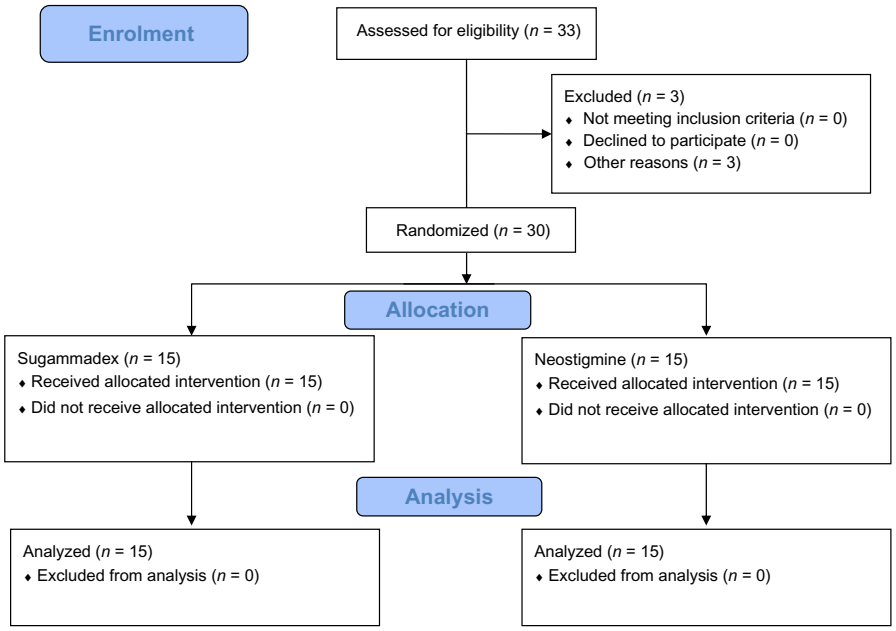

Fig. 1. CONSORT flow diagram.

Statistical analysis

Demographic data were analyzed with unpaired *t*-test. ASA classification and the type of surgery were analyzed with Fischer's exact test. All statistical analyses were performed using SPSS for Windows software (version 17.0, SPSS, Inc., Chicago, IL, USA). Based on our preliminary data (not published), we assumed a mean maximal change of 15 [standard deviation (SD) 7.5] SE units in patients receiving sugammadex. Vasella and coworkers[11] discovered a mean maximal change of 7 (SD 7.5) BIS units after administration of neostigmine. Because agreement between BIS and Entropy has been shown to be good in paralyzed patients,[19] we assumed a mean maximal change of 7 (SD 7.5) SE units in patients receiving neostigmine. We calculated the sample size using the level of statistical significance as $\alpha = 0.05$ and $\beta = 0.2$. Fifteen patients were needed in both groups to test our hypothesis. Statistical significance was defined as $P < 0.05$.

Results

Thirty-three patients were recruited for the study. The operation was cancelled in two patients, and one operation was rescheduled for a later date. Thirty patients were randomized; all received the assigned study treatment (Fig. 1). Patient characteristics did not differ between the study groups (Table 1). The degree of NMB at the time of NMB reversal, and the estimated effect-site concentrations of propofol and remifentanil during the reversal of NMB are presented in Table 2.

Table 1

Patient characteristics.

	Sugammadex ($n = 15$)	Neostigmine ($n = 15$)
Age	42 (9)	45 (13)
ASA I/II	12/3	9/6
Weight (kg)	67 (11)	65 (8)
Height (cm)	166 (4)	165 (7)
Laparoscopy	7	8
Laparotomy	8	7

Values are mean (SD) or number.
ASA, American Society of Anesthesiologists.

Table 2

The degree of neuromuscular block and estimated effect-site concentrations of propofol and remifentanil at the time of neuromuscular blockade reversal.

	Sugammadex	Neostigmine	*P*-value
NMT count 1/2/3/4	0/0/1/14	0/1/0/14	0.96
TOF ratio (%)	9 (0–44)	27 (3–61)	0.15
Propofol Ce (mcg/ml)	2 (2–5)	2 (2–3.5)	0.52
Remifentanil Ce (nanog/ml)	1 (0.5–2)	1 (0.5–2.5)	0.47

Data presented as number, or median (range).
Ce, effect-site concentrations; TOF, train of four.

Reversal of NMB with sugammadex produced a strong response in five patients, a weak response in four patients and no response in six patients. Administration of neostigmine produced a strong response in five patients, a weak response in one

Table 3

The numerical changes in SE, RE, RE-SE, BIS and BIS EMG produced by different responses.

	Strong response ($n = 5 + 5$)	Weak response ($n = 4 + 1$)	No response ($n = 6 + 9$)
SE	41 (8) →87 (3)	48 (7) →68 (6)	44 (7) →53 (7)
RE	50 (10)→99 (2)	49 (7) →87 (10)	45 (8) →58 (9)
RE-SE	9 (7) →31 (5)	1 (0) →25 (6)	2 (3) →10 (9)
BIS	45 (12)→85 (5)	54 (20)→71 (18)	41 (12)→53 (14)
BIS EMG (dB)	34 (8) →53 (4)	33 (7) →47 (16)	27 (4) →32 (7)
Laparoscopy/laparotomy	7/3	2/3	6/9

Value are mean (SD) or number.
BIS, bispectral index; BIS EMG, BIS electromyographic; RE, Response Entropy; SD, standard deviation; SE, State Entropy.

patient and no response in nine patients (NS). The changes in the numerical values SE, RE, RE-SE, BIS and BIS EMG produced by different response types are presented in Table 3. The changes in EEG in one study patient produced by strong EMG activation and the resulting rise in the numerical values of BIS, BIS EMG and Entropy are demonstrated in Fig. 2.

In patients with a strong response, a more detailed analysis was done to discover possible differences between sugammadex and neostigmine. At the time of NMB reversal, there was no statistically significant difference in the numerical values of SE, RE, RE-SE or BIS EMG between patients receiving sugammadex and neostigmine. However, the BIS values [mean (SD)] were higher in patients receiving sugammadex than in patients receiving neostigmine, 53 (8) vs. 38 (10) ($P < 0.05$). The time period [mean (SD)] from administration of the study drug to the maximal SE value was 110 (37) s and 218 (56) s in patients receiving sugammadex and neostigmine, respectively ($P < 0.01$).

The correlation coefficient between the degree of NMB at the time of the study drug and the response type was 0.29 (NS).

When the Entropy biosignal was analyzed in detail, our analysis revealed that the increase in the numerical values of SE, RE and BIS was most likely caused by the appearance of EMG in the biosignal. There were eight patients (four received sugammadex and four received neostigmine) who showed no signs of EMG during the 5-min study period. In three out of these eight patients, a transient change in EEG was detected; all these received neostigmine. The change appeared approximately 60 s after administration of neostigmine and lasted for 15–20 s. In spectral analysis, this change caused an increase in relative delta power and a decrease in relative alpha and beta powers. There was also a decrease in SEF95. However, this transient change in EEG did not cause a change in the numerical values of BIS or Entropy. The whole 5-min study period in one patient without EMG is depicted in Fig. 3.

Discussion

The first finding in our study was that reversal of NMB by sugammadex or neostigmine during light propofol-remifentanil anesthesia may increase the numerical values of BIS and Entropy. This finding is in line with the earlier results of Vasella and coworkers,[11] but somewhat different from the findings of Illman and coworkers.[10] In their conclusion, Vasella and coworkers stated that the increase in the numerical values of BIS {7 (7.5) BIS units [mean (SD)]} was supportive of the de-afferentation theory. Interestingly, also the BIS EMG values [mean (SD)] increased in the study by Vasella and coworkers from 28 (1) dB to 31 (5) dB, but they concluded that this increase was unlikely to be responsible for the increasing BIS values. The anesthetic regimen in our study was similar to the regimen of Vasella and coworkers, but the analysis of the BIS and Entropy values was different. In Vasella's study, the BIS values were averaged over 1 min, and only the numerical values of BIS and BIS EMG were analyzed. In this study, we used the maximal values, and we also analyzed the actual biosignal recorded by the Entropy strip. In our opinion, it is reasonable to say that our approach is more accurate in detecting the cause behind rising BIS and Entropy values. The discrepancy between our results and those of Illman and coworkers are most likely due to the deeper level of anesthesia in their study.

Our second finding was that the increase in BIS and Entropy values appears more rapidly after administration of sugammadex than after administration of neostigmine. This finding can be explained by the faster mechanism of action of sugammadex.[20] However, this subset of patients consisted of only ten (5 + 5) patients, too small a number for proper

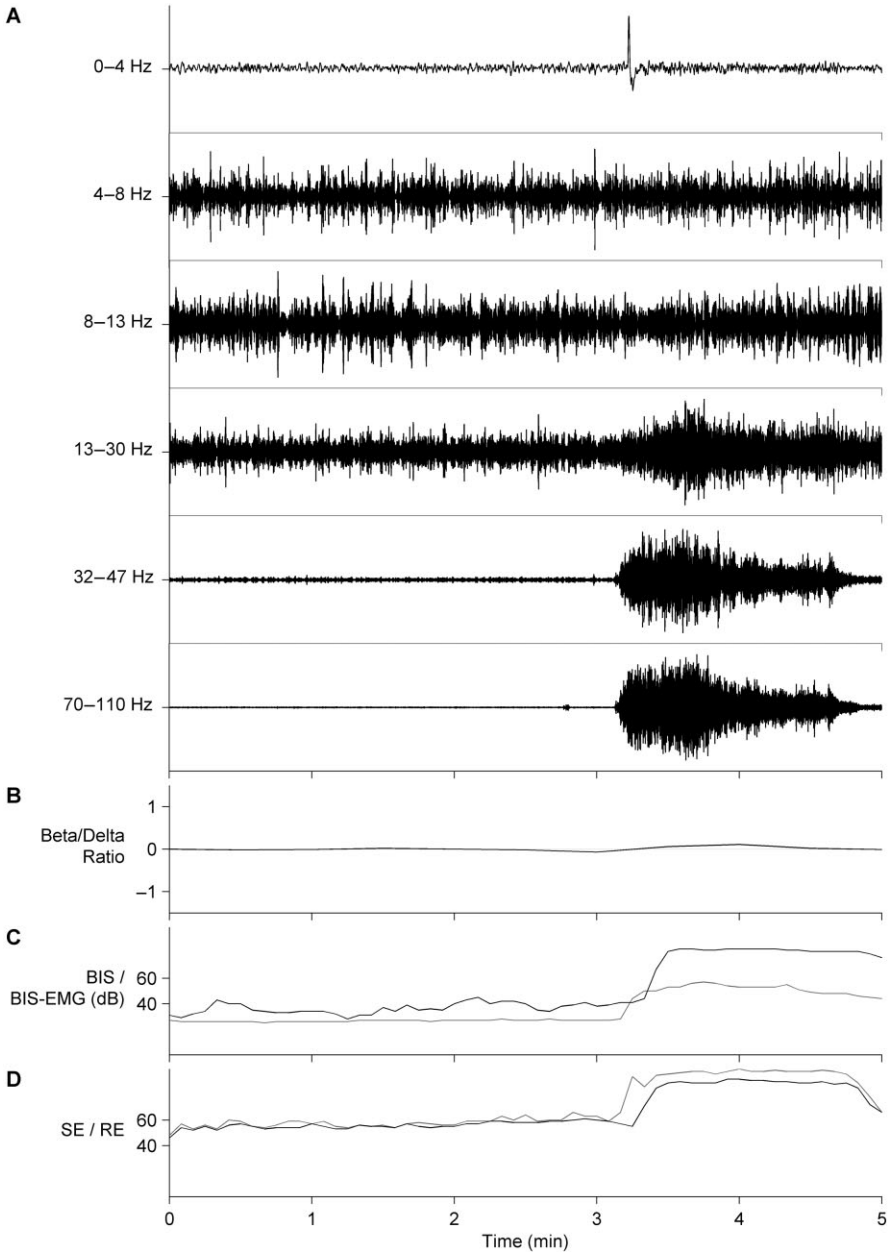

Fig. 2. The whole 5-min study period in one patient with a strong response. The reversal agent (neostigmine) was given at time point 0. (A) The band-pass filtered electroencephalogram from 0–4 (delta), 4–8 (theta), 8–13 (alpha), 13–30 (beta), 32–47 [Response Entropy-State Entropy (RE-SE)] and 70–110 [bispectral index electromyographic (BIS EMG)] Hz frequency bands, plotted strongly compressed to demonstrate amplitude changes. A strong EMG activation approximately 3 min 10 s after neostigmine produces changes in the 32–47 and 70–110 Hz frequency bands, as expected, but also a change in the 13–30 Hz frequency band. This change in 13–30 Hz frequency band causes an elevation, in chronological order, in RE, BIS EMG, SE, and BIS (shown in C and D). (B) Beta/delta ratio is also slightly changed by the EMG arousal.

statistical power, but we regarded this detail as one more tool toward understanding the physiology behind strangely behaving SE and BIS values.

The third observation in our study was that the increase in BIS and Entropy values was most likely caused by EMG. Because the power spectra of EEG and EMG overlap in the frequency range of 10–50 Hz, a change in EEG activity cannot be ruled out whenever a strong EMG activity is present.[5,6] If the so-called de-afferentation theory is valid, it is theoretically possible that the arousal caused by the reversal of NMB has only a weak central effect not quantifiable at deeper levels of anesthesia. Also, in cases of strong EMG activity, a small change in EEG may not be visible underneath strong EMG activity. When we analyzed the episodes where no EMG was visible after reversal of NMB, we found a transient change in EEG. However, this change did not cause a change in the numerical values of BIS and Entropy. The cause of this transient change in EEG remains speculative. It may be caused by afferent input from the proprioceptors, thus supporting the de-afferentation theory. On the other hand, this change was detected only in patients receiving neostigmine so it may be caused by neostigmine itself (central cholinergic activation).

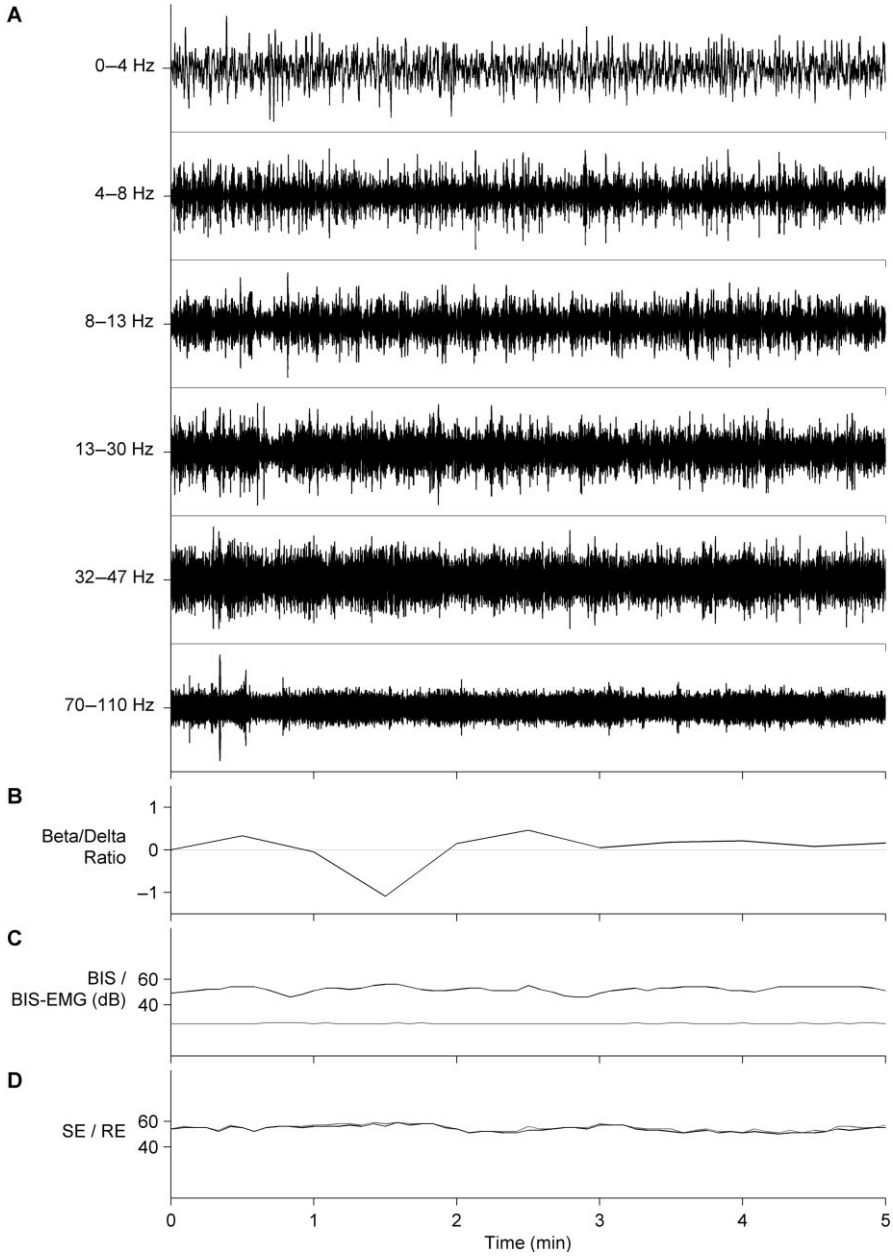

Fig. 3. The 5-min study period in a patient with no response. The reversal agent (neostigmine) was given at time point 0. From (A) to (D), the same parameters as in Fig. 2. This time, no electromyographic (EMG) arousal is visible, and no change in the numerical values of bispectral index electromyographic (BIS) or Entropy is seen. However, there is a change in beta/delta ratio approximately 90 s after study drug. The cause of this change in beta/delta ratio is unclear. RE, Response Entropy; SE, State Entropy.

This is the first study to compare the effects of sugammadex and neostigmine on the numerical values of BIS and Entropy. To discover the electroencephalographic and EMG phenomena that explain the increase in the numerical values of BIS and Entropy, we also analyzed the biosignal recorded by the Entropy strip. In our opinion, this is one of the strengths of this study. So far, all the previous studies have focused only on the numerical values of BIS and Entropy.

There are limitations to our study. One obvious limitation of this study is that the collection and analysis of the biosignal is possible only from the Entropy sensor not from the BIS sensor. Because the two sensors were placed contralaterally, it is possible that they may register information differently. For example, if the activated motor unit is directly under one of the sensors, the motor unit potential will affect one sensor more strongly than the other sensor. Therefore, the biosignal recorded by the Entropy sensor may be different from the biosignal recorded by the BIS sensor. If it was possible to collect the biosignal from the BIS sensor, one would have one more tool to discover the truth behind strangely behaving numerical BIS values.

There was no placebo group in our study, which may be regarded as a limitation. Because propofol and remifentanil were administered with TCI and the estimated effect-site concentrations were kept unchanged after administration of the study drug, in our opinion, it was justified to have no placebo group. Also, the light level of NMB at the time of reversal, at least in some patients, can be regarded as a limitation. In our institution, unnecessarily deep levels of NMB are avoided so our study protocol reflects the daily clinical routine of our institution. This study was designed to answer a question raised by a clinical observation, so the best way to find an answer would be to study patients in the same clinical settings. It must also be kept in mind that administration of neostigmine is not safe during profound levels of NMB. Finally, as the frontal muscles are more resistant to NMB than the peripheral muscles, it can be argued that the degree of NMB registered at the adductor pollicis muscle does not reflect the degree of NMB at the frontal muscles.

In normal conditions, when blood-brain barrier (BBB) is intact, neither neostigmine nor sugammadex cross the BBB. Recently, Inoue and coworkers reported a case of prolonged recovery from general anesthesia with sevoflurane after a neurosurgical operation, where the recovery from general anesthesia was achieved by administration of neostigmine.[21] Our patients were undergoing gynecological operations; therefore, it is reasonable to assume that the BBB was intact and that the central cholinergic activation is an unlikely cause for increasing BIS and Entropy values in our study. Central cholinergic activation has been mostly described after administration of fysostigmine, an anticholinesterase that is able to cross BBB. It should be kept in mind that the suppression of cholinergic activity in the central nervous system may be different when different anesthetics are used. Therefore, inhibition of central cholinergic activity after propofol-remifentanil anesthesia may be different from a situation where inhalational agents are used.[22,23] Overall, the inhibition of central cholinergic activity by general anesthesia and the activation of central cholinergic activity by reversal of NMB have not been studied in detail. In our opinion, the first step toward understanding the electrophysiology behind central cholinergic activation could be the analysis of multichannel EEG recording.

Another theoretical reason for increasing BIS and Entropy values after administration of sugammadex could be the capture of propofol and/or remifentanil by sugammadex. However, as the affinity of sugammadex for propofol and remifentanil is negligibly small, the capture of propofol and/or remifentanil by sugammadex is very unlikely.[9] Also, as the index values increased similarly in the neostigmine group, the reason for increasing index values is not explained by the pharmocodynamic action of sugammadex.

Finally, at least two confounding factors must be taken into account when interpreting our results. First, the type of surgery may have an effect on the nociceptive-antinociceptive balance of the patient after the operation, i.e. patients after laparotomy can be more likely to show signs of arousal than patients after laparoscopic procedures. In this study, both groups had an almost identical number of laparotomies and laparoscopies. In addition, when we analyzed the different response types according to the type of surgery, there was no correlation between the type of surgery and the type of response (strong/weak/no response). Second, the degree of neuromuscular block at the time of NMB reversal may be another confounding factor. We also compared the degree of NMB with the type of response and found no correlation.

In conclusion, our data suggest that reversal of NMB with sugammadex or neostigmine during light propofol-remifentanil anesthesia may increase the numerical values of BIS and Entropy. This increase in the numerical values of BIS and Entropy is most likely caused by increased EMG activity. However, neostigmine also produced a transient change in EEG without elevating BIS or Entropy values.

Conflict of interest: Arvi Yli-Hankala is a paid consultant for GE Healthcare Finland.

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Can electromyographic arousal be detected visually on the Datex-Ohmeda S/5™ Anesthesia Monitor?

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Background: Electroencephalogram (EEG)-based depth of anaesthesia monitoring is susceptible to contaminating electromyographic (EMG) activity. Many authorities have suggested that anaesthesiologists using these monitors should interpret the raw EEG waveform seen on the anaesthesia monitor.
Methods: In 34 patients anaesthetized with propofol using two doses of rocuronium (0.6 and 1.2 mg/kg), we studied whether the EMG arousal can be detected visually on the anaesthesia monitor. The Bispectral Index (BIS) and Entropy biosignals on the monitor were recorded with a video camera, and the one-channel EEG recorded by the Entropy strip was collected on a laptop computer. The recordings and the one-channel EEG were analyzed offline by two experts (anaesthesiologist and neurophysiologist), both with a long experience on anaesthesia-related EEG.
Results: EMG arousal existed in 14/34 and 13/33 patients in the BIS and Entropy biosignals, respectively. The anaesthesiologist detected EMG on the monitor in 7/14 patients with BIS (sensitivity 50%) and in 4/13 patients with Entropy (31%). The clinical neurophysiologist detected EMG in 6/14 (43%) patients with BIS and in 5/13 (38%) with Entropy. The specificity of the EMG analyses was 55 and 65% with BIS, and 85 and 90% with Entropy. EMG arousal was detected in BIS biosignal in 10/17 and 4/17 patients with 0.6 and 1.2 mg/kg doses of rocuronium ($P = 0.04$).
Conclusions: In contrast to many EEG phenomena, EMG activity cannot be accurately detected visually from the raw EEG on the anaesthesia monitor. Further development in the quality of the anaesthesia monitors is warranted.

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The Bispectral Index (BIS™, Covidien, Boulder, CO, USA)[1] and Entropy (M-Entropy™ module, GE Healthcare, Helsinki, Finland)[2] are two commercially available methods for measuring the hypnotic component of anaesthesia. The BIS monitor produces four parameters on the anaesthesia monitor: BIS index scaled from 100 (awake) to 0 [suppressed electroencephalogram (EEG) signal], signal quality index (BIS SQI), electromyographic (BIS EMG) activity and suppression ratio. In the analysis of EMG activity, BIS utilises the 70–110 Hz bandwidth. The information produced by Entropy on the anaesthesia monitor includes State Entropy (SE) scaled from 91 (awake) to 0 (EEG suppression), Response Entropy (RE) scaled from 100 to 0, and burst suppression ratio. SE is calculated from the 0.8–32 Hz frequency band, which is thought to include mainly the EEG component of the collected signal. RE is calculated using the 0.8–47 Hz frequency band. The difference between RE and SE (RE–SE) is thought to reflect EMG activity, a sign of impending arousal or inadequate anaesthesia.[3]

The location of the recording electrodes is on the forehead in both BIS and Entropy. As the collected signal is always a combination of EEG and EMG, EMG activity is a potentially confounding factor in BIS and Entropy monitoring. EMG has shown to elevate the numerical values of BIS and Entropy,[4–6] even at burst suppression level.[7] Recently, several authorities have suggested that the anaesthesiologists relying on the EEG-based depth of anaesthesia monitors should be capable of interpreting the original biosignal instead of relying solely on the numerical values of the monitor.[7–12]

We wanted to investigate using today's standard operating room technology if it is possible to reliably detect EMG arousal visually on the anaesthesia monitor. Strong EMG arousal may increase the

numerical values of BIS and Entropy, and therefore lead to overdosing of anaesthetic agents. If it were possible to detect EMG arousal visually on the anaesthesia monitor, the overdosing of the anaesthetic agents could be avoided. The standard in our study was the one-channel EEG recorded by the Entropy strip, and the study object was the raw biosignal on the anaesthesia monitor, recorded with a high-definition (HD) video camera and analysed offline. The primary end point in this study was the accuracy of the raw EEG signals of BIS and Entropy (on the anaesthesia monitor) in the detection of EMG arousal, when compared against the traditional standard, one-channel EEG recorded by the Entropy strip. The secondary end point was the incidence of EMG arousal during intubation using two different doses of rocuronium.

Methods

Patients

After approval from the Ethics Committee of Tampere University Hospital (R08197M) and from the Finnish National Agency for Medicines (KLnro 249/2008), the study was registered with EudraCT (2008–008129-31). The study was also registered with http://www.ClinicalTrials.gov under the US National Library of Medicine (Code NCT01142635).

Thirty-four women undergoing gynaecological operations were enrolled in this prospective, double blind, and randomised study. Patient enrolment started 2 March 2009 and ended 29 March 2010. Before any patients were enrolled in the study, sealed envelopes containing the assigned dose of rocuronium were dropped into a cardboard box, and the envelopes were carefully mixed. On the day of the operation, an envelope was lifted from the box by the anaesthesiologist in charge of the anaesthesia (A. A.). The envelope was handed to an operating room nurse, who thereafter prepared the study drug in the absence of the anaesthesiologist in charge. The patient material is partly the same as in our earlier study comparing the effects of sugammadex and neostigmine in the reversal of neuromuscular blockade (NMB); 29 of these patients were also enrolled in that study.[6] Written informed consent was obtained from all patients. Eligible patients were assigned an allocation number and randomised to a treatment. Inclusion criteria were an American Society of Anesthesiologists (ASA) score of I or II, body mass index < 30, age 18–65 years. Exclusion criteria were disease or injury affecting central nervous system, alcohol or drug abuse and allergy to any of the drugs used during anaesthesia. All patients fasted overnight before surgery.

Anaesthesia protocol

Approximately 60 min before induction of anaesthesia, the patients were pre-medicated with diazepam 10 mg orally. After arrival to the operating theatre, an intravenous route was established, and an infusion of isotonic saline was started. Standard monitoring included non-invasive blood pressure every 5 min, a three-lead electrocardiogram, inspired fractions (Fi) and end-tidal (Et) concentrations of oxygen, inspiratory and end-tidal partial pressure of carbon dioxide, peripheral pulse oximetry, and NMB monitoring with M-NMT Mechanosensor™ (GE Healthcare, Helsinki, Finland). The patients were monitored with the Datex-Ohmeda S/5™ Anesthesia Monitor (GE Healthcare, Helsinki, Finland). All patients were anaesthetised with a target-controlled infusion (TCI, Asena™ PK, Alaris Medical Systems, Basingstoke, UK) of propofol. Pharmacokinetic model of Schnider[13] was used for administration of propofol. Effect-site concentration (Ce) of propofol was adjusted according to the judgement of the anaesthesiologist (A. A.) in charge. To facilitate endotracheal intubation, the patients were randomised to receive rocuronium bromide (Esmeron®, N.V. Organon, Oss, the Netherlands) either 0.6 or 1.2 mg/kg. An operating room nurse prepared the different rocuronium solutions in the absence of the anaesthesiologist in charge of the anaesthesia. In the group receiving rocuronium 0.6 mg/kg, 5 ml of rocuronium (original concentration 10 mg/ml) was diluted to a volume of 10 ml, yielding a solution containing 5 mg/ml of rocuronium. In the group receiving rocuronium 1.2 mg/kg, a 10-ml syringe was filled with undiluted rocuronium. Thus, both patient groups were given the study drug 1.2 ml/10 kg. Rocuronium was given only after the estimated effect-site concentration of propofol had reached steady state. Endotracheal intubation was performed when train of four counts was 0/4.

BIS and Entropy monitoring

The monitoring of BIS and Entropy started before induction of anaesthesia and continued uninterrupted during the whole study period. For BIS monitoring, a disposable BIS Quatro™ sensor (Covidien, Boulder, CO, USA) and E-BIS module for S/5™ Anesthesia Monitor (GE Healthcare, Helsinki, Finland) were used. The scale of BIS on the anaesthesia monitor was set to 100 μV. For Entropy

monitoring and one-channel EEG recording, a disposable Entropy electrode strip (Entropy Sensor, GE Healthcare) was used. After the forehead skin was degreased with 70% isopropanol, the strips were positioned as recommended by the manufacturers. The sensors were randomly positioned so that the first sensor was placed lower on the forehead and on the left temple, and the second sensor was placed above the first sensor on the forehead, and then on the right temple. The temporal electrodes were positioned 2 cm laterally from the outer canthus of the eye. The frontal electrodes were on the frontal muscle, recording EEG from frontal pole, and the temporal electrodes were on the orbicularis oculi and temporal muscles, recording EEG from frontal and temporal lobes, including basal forebrain and mesial temporal cortex. All monitored parameters were obtained from the monitor at 5-sec intervals with S5 Collect software (GE Healthcare, Helsinki, Finland) and saved on a laptop computer. The EEG was collected with an Entropy Module of the S/5™ Anesthesia Monitor, with a sampling rate of 400 Hz. High and low pass filters of 0.5 and 118 Hz (–3 dB; 60 dB/decade), respectively, were applied. Power line artefact at 50 Hz was not filtered. The scale of Entropy on the anaesthesia monitor was set to 100 μV.

Technical data of the study equipment

The study equipment was chosen so that as little data as possible would be lost due to technical reasons. Resolution of the S/5 Anesthesia Monitor display is 1024×768. The visible BIS and Entropy biosignals were recorded in full HD with a video camera (Sony Handycam® HDR-SR10E, Sony Inc., Tokyo, Japan). This video camera records the video clips in Advanced Video Codec High Definition (AVCHD) format (resolution 1920×1080). In the visual analysis of the HD recordings of BIS and Entropy, a laptop computer was used (HP EliteBook 8730w, resolution of the screen 1920×1080, Hewlett–Packard, Palo Alto, CA, USA).

EMG analysis of BIS and Entropy

In the analysis of BIS, the rise in the BIS EMG numerical values ≥ 35 was considered as a 'true' EMG arousal. In the detection of EMG in the BIS HD video recordings, the typical spiky, high-frequency EMG pattern was used to judge whether EMG was present or not.

In the analysis of Entropy, the one-channel EEG recorded by the Entropy strip was used as a reference. In all the patients, the one-channel EEG before and after intubation was analysed visually, by calculating power spectra, and by plotting spectrograms. The typical EMG pattern in the original biosignal, with a characteristic change in spectrogram, and a considerable power increase of above 40 Hz, was regarded as a 'true' EMG arousal to intubation. As with BIS, the absence or presence of EMG in the Entropy HD recordings was based on the typical spiky, high-frequency EMG pattern.

Spectrogram yields the same information as successive power spectra. Spectrograms were produced with Somnologica™ sleep analysis program (Medcare Flaga, Reykjavik, Iceland). In this study, consecutive 1.0-sec samples were calculated and presented vertically along y-axis. These consecutive power spectra were plotted against time along x-axis. The amount of activity at respective frequencies is seen as darkness (density) of the spectrogram.

The HD recordings of BIS and Entropy were analysed blindly by an anaesthesiologist (A. Y.-H.) and by a clinical neurophysiologist (V. J.), both with a long experience on the anaesthesia-related EEG. The analyses were performed separately so that both analysts were unaware of each others' results and of the dose of rocuronium. During the analysis of the recorded BIS biosignal, the recorded Entropy biosignal was hidden from the view, and vice versa. Only the biosignal on the monitor was shown in the analysis of HD video recordings, that is, the numerical values of BIS and Entropy, as well as the bars indicating BIS EMG and BIS SQI were not visible during analysis.

Statistical analysis

Demographic data were analysed with t-test. ASA classification was analysed using Fisher's exact test, and the agreement between the two analysts was analysed by calculating Cohen's kappa coefficient. All statistical analyses were performed using SPSS for Windows software (version 17.0, SPSS, Chicago, IL, USA). Based on our previous data (intubation data not published), we assumed that intubation would cause EMG arousal in 55% of the patients receiving 0.6 mg/kg of rocuronium.[5] Based on the results of Kawaguchi and co-workers,[14] we assumed intubation-associated EMG arousal in 10% of the patients receiving 1.2 mg/kg of rocuronium. We calculated the sample size using the level of statistical significance as $\alpha = 0.05$ and $\beta = 0.2$. Fifteen patients were needed in both groups to test our hypothesis. To allow for dropouts, we decided to increase the group size to 17. Statistical significance was defined as $P < 0.05$.

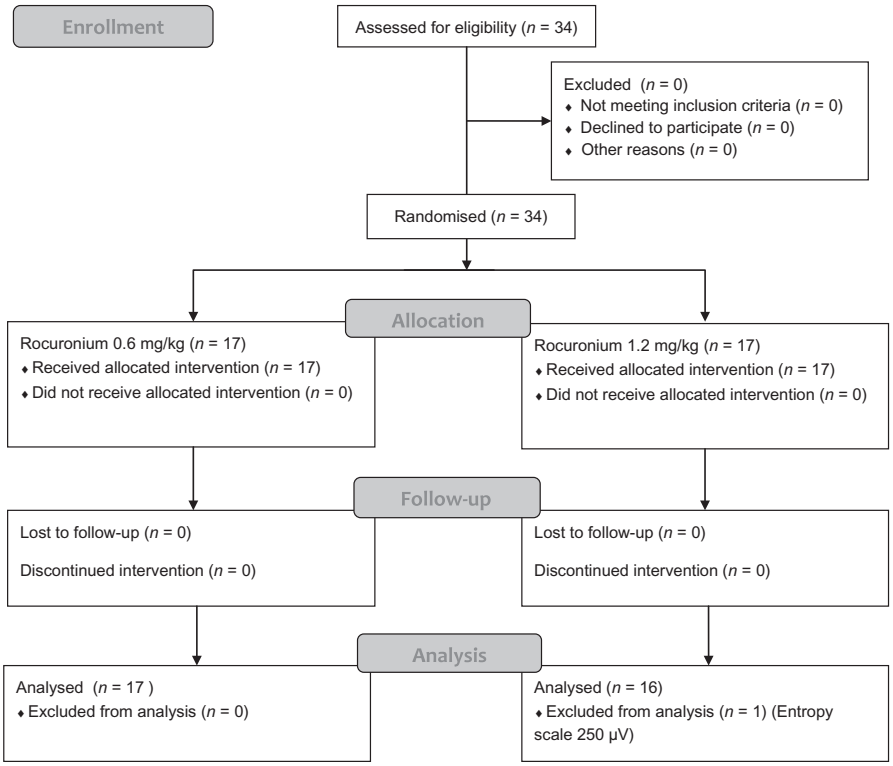

Fig. 1. CONSORT flow diagram.

Table 1

Patient characteristics. Values are mean (SD) or number.

–	Rocuronium 0.6 mg/kg ($n = 17$)	Rocuronium 1.2 mg/kg ($n = 17$)
Age	40 (12)	46 (12)
ASA I/II	13/4	11/6
Weight (kg)	69 (6)	65 (8)
Height (cm)	167 (6)	163 (5)

ASA, American Society of Anesthesiologists.

Results

A total of 34 (17 + 17) patients were recruited for the study. In one patient receiving rocuronium 1.2 mg/kg, the Entropy scale on the anaesthesia monitor was accidentally 250 µV; this patient was left out of the Entropy analyses (Fig. 1). Patient characteristics are shown in Table 1. The mean (standard deviation) estimated effect-site concentration of propofol at the time of intubation was 5.5 (0.71) and 5.76 (0.83) µg/ml in patients with 0.6 and 1.2 mg/kg of rocuronium, respectively (NS).

In the analysis of the Entropy biosignal with spectrogram, spectral analysis and visual analysis, strong EMG arousal causing SE value > 60 was detected in three patients (all these received 0.6 mg/kg of rocuronium). The anaesthesiologist detected the strong EMG arousal in 2/3 patients in both Entropy and BIS biosignals. The clinical neurophysiologist detected the strong EMG arousal in Entropy and BIS biosignals in 3/3 and 2/3 patients, respectively. When also the weaker intubation-associated EMG arousals were taken into account, EMG arousal could be detected in a total of 9/17 and 4/16 patients receiving 0.6 and 1.2 mg/kg of rocuronium, respectively ($P = 0.18$). The intubation-associated changes in the numerical values of BIS and Entropy are shown in Fig. 2.

In the analysis of BIS (BIS EMG ≥ 35 dB), EMG arousal could be detected in 10/17 and 4/17 patients receiving 0.6 and 1.2 mg/kg of rocuronium, respectively ($P = 0.04$).

The accuracy of the two blinded investigators in detecting EMG in the full HD recordings of BIS and Entropy is depicted in Tables 2 and 3. The inter-rater agreement between the two observers is seen in Table 4. Both observers noticed an odd-looking artefact in a total of 10 BIS signals on the monitor. In addition to the true positive detections of EMG arousal, a total of 23 false positive EMG detections were made by the observers (12 by the anaesthesiologist, 11 by the clinical neurophysiologist).

Discussion

The main finding in our study is that intubation-associated EMG arousal cannot be reliably detected visually on the S/5™ Anesthesia Monitor. Strong

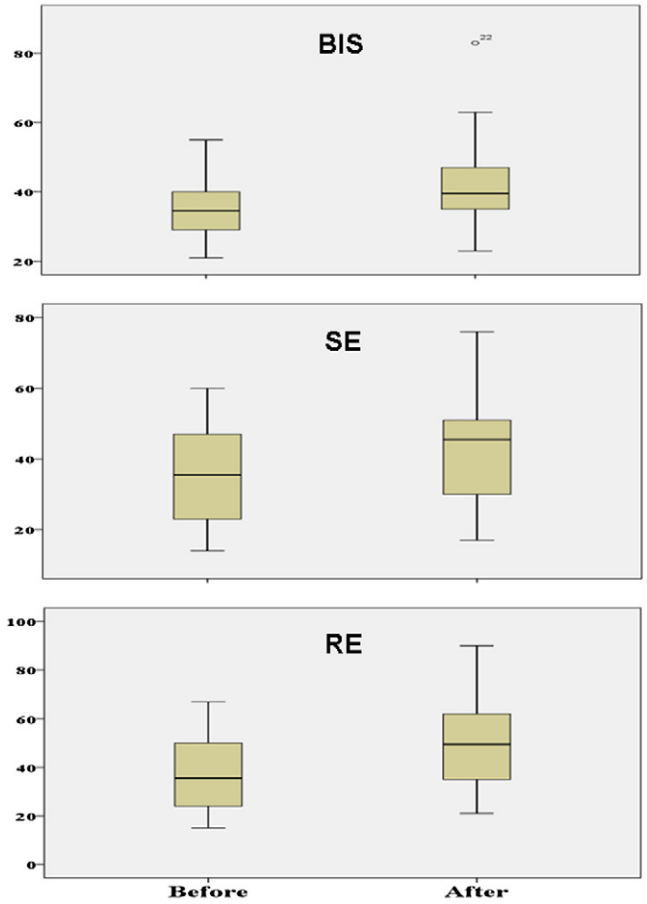

Fig. 2. The numerical values of Bispectral Index (BIS) and Entropy before and after intubation. Values presented as median, 25th and 75th percentiles, and range. SE, State Entropy; RE, Response Entropy.

EMG arousal (causing SE value to rise > 60) was quite well (2 of 3 cases) detected by both observers. However, strong EMG arousal appeared in only three patients, too small a number for proper statistical power. Most EMG arousals in this study were weaker (SE remained < 60), a phenomenon less likely to lead the anaesthesiologist in a wrong direction, that is, to increase the amount of anaesthetic given to the patient. An additional finding in this study was that the incidence of EMG arousal was almost as frequent with 0.6 and 1.2 mg/kg doses of rocuronium.

The main finding does not fully support the often-heard statement that it is possible for the anaesthesiologist in charge of the anaesthesia to interpret the raw biosignal on the anaesthesia monitor correctly, at least in the case of EMG arousal.

The clinical relevance of the correct visual detection of EMG arousal is that potential overdosing of anaesthetic agents may be avoided. As mentioned earlier, strong EMG arousal has shown to increase the numerical values of BIS and Entropy. If the increase in the numerical values of BIS and Entropy (caused by EMG arousal) is not properly interpreted and leads to an increase in the amount of anaesthetic administered to the patient, the patient may become exposed to overdosing of anaesthetic agents, and therefore, to potential side effects (hypotension, delayed recovery, post-operative nausea and vomiting). In our opinion, the main goal in the observation of the raw EEG signal during general anaesthesia is to recognise the underlying 'basic' pattern of the EEG, which is sometimes camouflaged by strong EMG activity.

Several limiting factors must be taken into account when contemplating this finding. First, it may be argued that EMG arousal would have been detected more accurately if the scales of BIS and Entropy had been set to 50 μV. If the scale had been set to 50 μV, the scale would have been too small for EEG-related fluctuations, cutting off substantial parts of the biosignal. Thereafter, a full analysis of the biosignal would have been impossible. In this study, the scale of 100 μV was considered appropriate, sensitive enough for detection of EMG, but allowing a full visual analysis of the biosignal. Whether EMG arousal could be more accurately detected using the scale of 50 μV remains to be seen in future studies.

Second, there are well-known artefacts that make visual interpretation of the one-channel EEG on the anaesthesia monitor very challenging. For example, the 50 Hz power line artefact, although not influencing the numerical values of BIS and Entropy, may appear on the anaesthesia monitor very identical to EMG activity. In one patient in our study, the 50 Hz power line artefact (visible both in BIS and in Entropy biosignals) was interpreted as EMG arousal both by the anaesthesiologist and by the clinical neurophysiologist. In the detailed analysis of the recorded one-channel EEG, it was easy to detect the 50 Hz power line artefact and remove it by filtering (Fig. 3). Based on the information provided by Fig. 3, it can be argued that frequency domain analysis of EEG (power spectrum), when shown in real time on the anaesthesia monitor, offers relevant information when an anaesthesiologist is interpreting the raw signal. By adding frequency domain analysis of EEG on the anaesthesia monitor, substantial improvement could be made to today's 'standard' EEG-based depth of anaesthesia monitoring. In Fig. 4, the importance of frequency domain analysis of EEG is further emphasised; without the help of

Table 2

Accuracy of the two analysts in detecting electromyographic arousal in Bispectral Index biosignal.

BIS						
Detected EMG		True EMG		Total	Sensitivity	Specificity
Anaesthesiologist		Yes	No			
	Yes	7	9	16	7/14 = 50%	11/20 = 55%
	No	7	11	18		
Total		14	20	34		
Clinical neurophysiologist	Yes	6	7	13	6/14 = 43%	13/20 = 65%
	No	8	13	21		
Total		14	20	34		

Table 3

Accuracy of the two analysts in detecting electromyographic (EMG) arousal in Entropy biosignal.

Entropy						
Detected EMG		True EMG		Total	Sensitivity	Specificity
Anaesthesiologist		Yes	No			
	Yes	4	3	7	4/13 = 31%	17/20 = 85%
	No	9	17	26		
Total		13	20	33		
Clinical neurophysiologist	Yes	5	2	7	5/13 = 38%	18/20 = 90%
	No	8	18	26		
Total		13	20	33		

Table 4

Inter-rater agreement with Bispectral Index (BIS) and Entropy biosignals.

BIS					
Detected EMG		Anaesthesiologist		Total	Inter-rater agreement (Cohen's kappa coefficient)
Clinical neurophysiologist		Yes	No		
	Yes	7	6	13	0.12 (slight agreement)
	No	9	12	21	
Total		16	18	34	
Entropy					
Detected EMG					
Clinical neurophysiologist		Yes	No		
	Yes	5	2	7	0.72 (substantial agreement)
	No	8	18	26	
Total		13	20	33	

EMG, electromyography. BIS, Bispectral Index.

spectrogram/power spectrum, the EMG arousal could not be detected.

Third, it must be emphasised that the BIS signals in this study were produced by the E-BIS module for S/5™ Anesthesia Monitor. This may explain why both observers discovered a very odd-looking artefact in the BIS signal in quite many patients (Fig. 5). Careful attempts were made to discover what the origin of this artefact was. BIS SQI was > 80 during the whole analysis period in nearly all of these patients. Therefore, it is reasonable to assume that the artefact did not result from a poor placement of the BIS sensor. Owing to the fact that collection and detailed analysis of one-channel EEG from the BIS sensor is not possible in GE Healthcare's monitoring system, the true origin of the artefact remains speculative. It is theoretically possible that BIS signals produced by a genuine BIS monitor would have looked different from the signals produced by E-BIS module.

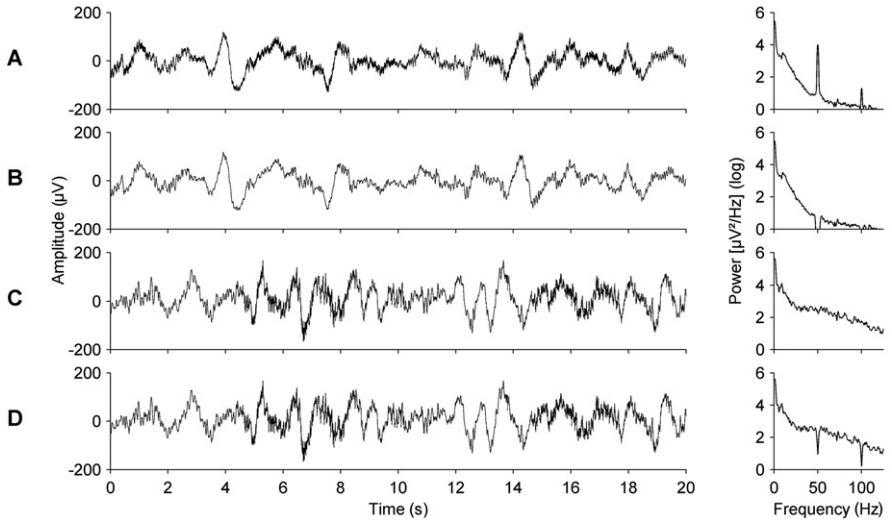

Fig. 3. (A) A 20-sec sample of the Entropy biosignal in one patient, interpreted by both analysts as electromyographic arousal. The power spectrum (not visible on the anaesthesia monitor) has a strong peak at 50 Hz, revealing the origin of the fuzziness of the biosignal as a power line artefact. (B) The same 20-sec sample of the biosignal after removal of the artefact by (47–53 Hz) filtering. After filtering, the peak at 50 Hz disappears, and visual inspection of the biosignal is possible. (C) A 20-sec sample of the Entropy biosignal and the respective power spectrum in a patient with true electromyographic (EMG) arousal. (D) The filtering leaves the EMG arousal visible in the biosignal, and the power spectrum is unchanged. Notice the similar visual appearance of power line artefact and EMG arousal in the respective biosignals. The power spectrum appears to be a useful tool for correct interpretation of the biosignal.

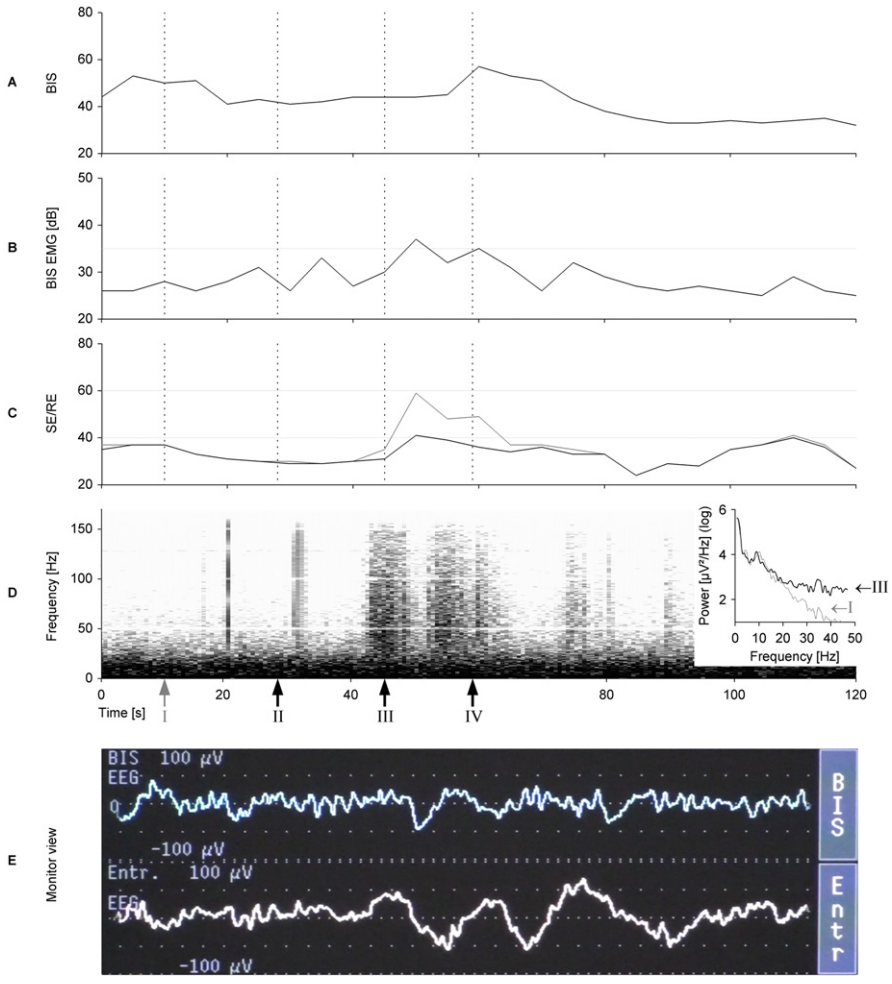

Fig. 4. Demonstration of the difficulty in detecting electromyographic (EMG) arousal visually on the anaesthesia monitor. (A), (B) and(C) The numerical values of BIS, BIS electromyographic (EMG) and Entropy, respectively, in one study patient. (D) In spectrogram and power spectrum, the changes caused by EMG arousal are detectable. I = time point before intubation without EMG. II = start of intubation. III = intubation-associated EMG arousal. IV = end of intubation. The two power spectra shown in D (labelled I and III) were calculated at time points I and III, respectively. (E) View of the anaesthesia monitor from time point III. EMG arousal is not detectable by visual interpretation of the BIS and Entropy biosignals.

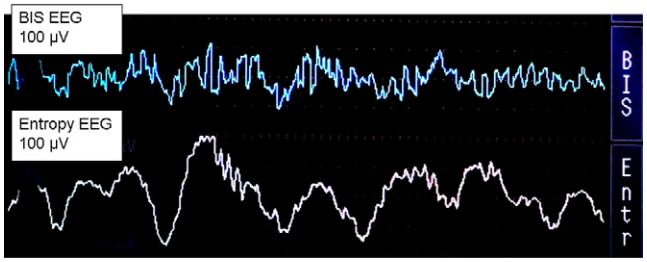

Fig. 5. Simultaneous Bispectral Index (BIS) and Entropy electroencephalogram (EEGs) on monitor screen, demonstrating an artefact in the BIS biosignal. The upper trace is the BIS biosignal, while the lower trace is Entropy EEG. A square-looking artefact on top of the BIS biosignal makes the interpretation of the information difficult. The lower trace (i.e., Entropy) shows mainly high-amplitude delta activity. Notice the very different appearance of the biosignals.

Finally, it must be kept in mind that the sampling frequency of the EEG signal from the Entropy module is 400 Hz. However, on the monitor screen, the waveform display sampling rate is 100 Hz. Therefore, antialiasing and downsampling are applied before displaying the waveform on the screen (personal communication from Kimmo Uutela, PhD, GE Healthcare Finland). Obviously, this may be the reason why the waveform on the anaesthesia monitor appears very different from the one-channel EEG collected on a computer for offline analysis, making the detection of EMG on the anaesthesia monitor very challenging.

All these above-mentioned limitations suggest that to properly analyse the EEG on the anaesthesia monitor, technological improvements must be made to today's standard monitoring equipment.

It must be emphasised that the presence or absence of EMG arousal was based on the numerical values of BIS EMG and on the analysis of the one-channel EEG registered by the Entropy. As the BIS and Entropy sensors were placed contralaterally, it is theoretically possible that they may register information differently.[15] By nature, EMG arousal is most likely present equally on both sides of the forehead. However, if the activated motor unit is directly under one electrode, the EMG arousal may be more clearly visible.[5] If the activated motor unit is more distant from the registering electrode, EMG may lose its sharp, spiky appearance, and its visual appearance may become very similar to EEG beta arousal.

Even though we have concluded that EMG arousal cannot be reliably detected visually on the S/5 Anesthesia Monitor, it must also be kept in mind that interpretation of the raw signal may be possible, and even desirable, in other clinical situations where index values behave contrary to traditional thinking. For example, the detection of burst suppression may be detected earlier by visual inspection than by relying on the numerical values of depth of anaesthesia monitors.[10] Also; the EEG delta arousal can easily be detected by analysing the raw biosignal, guiding a watchful anaesthesiologist in the right direction, thus avoiding the risks of too light an anaesthesia. Finally, it must be highlighted that the expert analysts performed the analyses without any knowledge about the numerical values of BIS or Entropy, nor did they have the bar indicating BIS EMG visible. In clinical practice, the anaesthesiologist is allowed to use the information provided by BIS EMG or, when using Entropy, RE–SE difference. With the help of these indicators of EMG activity, the correct interpretation of the raw signal (detection of EMG arousal) may be easier than in this study.

The additional finding in our study, that is, that EMG arousal was more frequent in patients receiving rocuronium 0.6 mg/kg than in patients receiving rocuronium 1.2 mg/kg, is in line with earlier results by Kawaguchi and co-workers.[14] The reason for a higher incidence of EMG arousal with the 1.2 mg/kg dose of rocuronium in our study can be explained by the different methods in EMG analysis. In our study, the one-channel EEG recorded by the Entropy strip was analysed both in time and in frequency domain to discover EMG arousal. In the study by Kawaguchi and co-workers, only RE–SE difference, a phenomenon thought to reflect EMG activity, was analysed. In our opinion, it is reasonable to claim that our approach may be more accurate in the detection of EMG arousal.

In conclusion, our study indicates that EMG arousal cannot be reliably detected on the standard anaesthesia monitor using the scale of 100 µV during propofol-rocuronium anaesthesia. In the quest for more accurate monitoring of the hypnotic component of general anaesthesia, technological improvements are warranted.

Conflict of interest: Professor Arvi Yli-Hankala is a paid consultant for GE Healthcare Finland.

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Table S1. CONSORT statement 2001 checklist: Items to include when reporting a randomized trial.

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